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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 mukożycz, powodującym wkomórkowy dozycie slubnych i srebnych przystępów masy ciała, lecz również zwiększone 6-krotne śmiertelność.

**Cel:** 1. Ocena przebiegu zaburzeń tolerancyjnych glukozy i cukrzycy u dzieci z mukożycydozą oraz efekty ich leczenia. 2. Ocena związku pomiędzy klasą mutacji w genie CFTR a tolerancją 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 Mukożycydozy Instytutu Matki i Dziecka w Warszawie. Pacjentów podzielono według kategorii zaburzeń tolerancyjnych glukozy w teście doustnego obciążenia glukozy (nieprawidłowa tolerancja glukozy, cukrzycy związaną z mukożycydozą bez hiperiglikemii na czczo, cukrzycza związaną z mukożycydozą z hiperglikemiią 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. Sześciu (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/3380delNGAG, G542X/2143delT).

** Wyniki:** U 7 (7/12) pacjentów z badanej grupy rozpoznano nieprawidłową tolerancję glukozy, u 5 (5/12) pacjentów cukrzycę związaną z mukożycydozą w tym u 4 pacjentów z hiperiglikemią na czczo u jednego bez hiperiglikemii na czczo. W trakcie obserwacji stwierdziliśmy u 4 (4/7) pacjentów z nieprawidłową tolerancją glukozy pogorszenie jej w kierunku cukrzyce bez hiperiglikemii na czczo. U 8 (8/12) pacjentów zastosowano insulinoterapię, w większości (5/8) pacjentów przy pomocy pompiny 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 mukożycydozą 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 mukożycydozy 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 pediatricznej chorych na mukożycydozą w Polsce są potrzebne, celem lepszego poznania związku pomiędzy zaburzeniami tolerancyjnymi glukozy, klasy mutacji w genie CFTR, wpływu metody leczenia zaburzeń tolerancji glukozy na stan kliniczny pacjentów.

**Słowa kluczowe:** cukrzyca związaną z mukożycydozą, insulin, 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,
consults 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, Tulsa, 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
each in 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
therapy. 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
decided 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
diabetes in our patients during follow up.
Table I. Characteristics of patients with IGT.  
*Tabela I. Charakterystyka pacjentów z nieprawidłową tolerancją glukozy.*

<table>
<thead>
<tr>
<th>Initials</th>
<th>CF (years)</th>
<th>Outpatient Clinic (years)</th>
<th>OGTT</th>
<th>Treatment</th>
<th>CFTR Gene Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age at onset</td>
<td>Age of referral to the Diabetes Outpatient Clinic (years)</td>
<td>Abnormalities in OGTT</td>
<td>Kind of treatment</td>
<td>(Class) Mutacje w genie CFTR (klasa)</td>
</tr>
<tr>
<td></td>
<td>of CF (years)</td>
<td>Wiek w momencie rozpoznania mukowiscydozy (w latach)</td>
<td>Nieprawidłowości w OGTT</td>
<td>Rodzaj leczenia</td>
<td></td>
</tr>
<tr>
<td>G.E.</td>
<td>1</td>
<td>11,38</td>
<td>IGT</td>
<td>Diet-insulintherapy (pump) Dieta-insulinoterapia (pompa)</td>
<td>Phe508del G542x (II/I)</td>
</tr>
<tr>
<td>O.P.</td>
<td>4/12</td>
<td>13,78</td>
<td>IGT</td>
<td>Insulintherapy (pens-pump) Insulinoterapia (peny-pompa)</td>
<td>Phe508del Phe508del (II/II)</td>
</tr>
<tr>
<td>K.M.</td>
<td>3/12</td>
<td>15,78</td>
<td>IGT</td>
<td>Diet-insulintherapy (pens) Dieta-insulinoterapia (penny)</td>
<td>G542x 2143delT (I/I)</td>
</tr>
<tr>
<td>J.K.</td>
<td>3/12</td>
<td>10,68</td>
<td>IGT</td>
<td>Diet-insulintherapy (pens) Dieta-insulinoterapia (penny)</td>
<td>Phe508del Phe508del (II/II)</td>
</tr>
<tr>
<td>D.M.</td>
<td>2/12</td>
<td>6,39</td>
<td>IGT</td>
<td>Diet Dieta</td>
<td>Phe508del N1303K (II/II)</td>
</tr>
<tr>
<td>U.M.</td>
<td>1/12</td>
<td>9,62</td>
<td>IGT</td>
<td>Diet Dieta</td>
<td>Phe508del Phe508del (II/II)</td>
</tr>
<tr>
<td>Z.M.</td>
<td>10</td>
<td>16,13</td>
<td>IGT</td>
<td>Diet / Diet</td>
<td>1717-1 2183AA-G (I/I)</td>
</tr>
<tr>
<td>Complications of CF and comorbidities</td>
<td>Dosage of insulin at the beginnig /end of treatment (u/kg/day)</td>
<td>Basal/bolus percentage at the beginning /end of treatment Percent insulin bazalnej /bolusowej na początku /końcu terapii (u/kg/dobę)</td>
<td>Circumstances of diagnosis of glucose abnormalities (screening, symptoms, exacerbations)</td>
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</tr>
<tr>
<td>Liver cirrhosis, exocrine pancreatic insufficiency Marskość wątroby, zewnątrzwydzielnicza niewydolność trzustki</td>
<td>0,59/1,35</td>
<td>(19/81)/(23/77)</td>
<td>Routine screening Badania przesiewowe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung transplantation due to chronic respiratory failure, liver cirrhosis, exocrine pancreatic insufficiency Transplantacja płuc z powodu przewlekłej niewydolności oddechowej, marskość wątroby, zewnątrzwydzielnicza niewydolność trzustki</td>
<td>0,33/0,30</td>
<td>(0/100)/(0/100)</td>
<td>Broncho-pulmonary exacerbations Zaosztrzenia choroby oskrzelowo- płucnej</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis, exocrine pancreatic insufficiency Młodzieńcze idiopatyczne zapalenie stawów, zewnątrzwydzielnicza niewydolność trzustki</td>
<td>0,55/0,96</td>
<td>(0/100)/(0/100)</td>
<td>Routine screening Badania przesiewowe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic respiratory failure, hepatosplenomegaly, exocrine pancreatic insufficiency Przewlekła niewydolność oddechowa, hepatosplenomegalia, zewnątrzwydzielnicza niewydolność trzustki</td>
<td>0,12/0,15</td>
<td>(0/100)/(0/100)</td>
<td>Broncho-pulmonary exacerbations Zaosztrzenia choroby oskrzelowo- płucnej</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exocrine pancreatic insufficiency Zewnątrzwydzielnicza niewydolność trzustki</td>
<td>-</td>
<td>-</td>
<td>Routine screening Badania przesiewowe</td>
<td></td>
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<tr>
<td>Exocrine pancreatic insufficiency Zewnątrzwydzielnicza niewydolność trzustki</td>
<td>-</td>
<td>-</td>
<td>Routine screening Badania przesiewowe</td>
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<tr>
<td>Exocrine pancreatic insufficiency Zewnątrzwydzielnicza niewydolność trzustki</td>
<td>-</td>
<td>-</td>
<td>Routine screening Badania przesiewowe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table II. Characteristics of patients with CFRD

<table>
<thead>
<tr>
<th>Initials</th>
<th>Age at onset of CF (years) Wiek w momencie rozpoznania mukowisciodyazy (w latach)</th>
<th>Age of referral to the Diabetes Outpatient Clinic (years) Wiek skierowania do Poradni Diabetologicznej (lata)</th>
<th>Abnormalities in OGTT Nieprawidłowości w OGTT</th>
<th>Kind of treatment Rodzaj leczenia</th>
<th>CFTR gene mutations (Class) Mutacje w genie CFTR (klasa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z.N.</td>
<td>3/12</td>
<td>17,3</td>
<td>CFRD FH(+)</td>
<td>Insulintherapy (pens-pump) Insulinoterapia (peny-pompa)</td>
<td>R553X 3380G&gt;A (I/I)</td>
</tr>
<tr>
<td>R.K.</td>
<td>3/12</td>
<td>14,53</td>
<td>CFRD FH(+)</td>
<td>Insulintherapy (pump) Insulinoterapia (pompa)</td>
<td>Phe508del G542x (II/I)</td>
</tr>
<tr>
<td>M.D.</td>
<td>3/12</td>
<td>8,82</td>
<td>CFRD FH(+)</td>
<td>Insulintherapy (pens-pump) Insulinoterapia (peny-pompa)</td>
<td>Phe508del Phe508del (II/II)</td>
</tr>
<tr>
<td>P.S.</td>
<td>7</td>
<td>7,46</td>
<td>CFRD FH(+)</td>
<td>Insulintherapy (pens) Insulinoterapia (peny)</td>
<td>Phe508del nieznana (II/unkown)</td>
</tr>
<tr>
<td>U.D.</td>
<td>2/12</td>
<td>13,16</td>
<td>CFRD FH (-)</td>
<td>Diet Dieta</td>
<td>Phe508del Phe508del (II/II)</td>
</tr>
<tr>
<td>Complications of CF and comorbidities</td>
<td>Dosage of insulin at the beginnin and end of treatment (u/kg/day)</td>
<td>Basal/bolus percentage at the beginnin and end of treatment</td>
<td>Circumstances of diagnosis of glucose abnormalities (screening, symptoms, exacerbations)</td>
<td></td>
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</tr>
</tbody>
</table>
| Lung transplantation due to chronic respiratory failure, exocrine pancreatic insufficiency | Transplantacja płuc z powodu przewlekłej niewydolności oddechowej, zewnątrzwydzielnicza niewydolność trzustki | 0,96/0,43 | Routine screening after lung transplantation  
Badania przesiewowe po transplantacji płuc |
| Exocrine pancreatic insufficiency | Zewnątrzwydzielnicza niewydolność trzustki | 1,04/1,50 | 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 odmowy płucnej, osteoporosa, marskość wątroby, zewnątrzwydzielnicza niewydolność trzustki | 0,25/1,22 | Broncho-pulmonary exacerbations  
Zaostrzenia choroby oskrzelo- płucnej |
| Exocrine pancreatic insufficiency | Zewnątrzwydzielnicza niewydolność trzustki | 0,51/0,83 | Loss of weight, broncho-pulmonary exacerbations  
Utrata masy, zaostrzenia choroby oskrzelowo-plucnej |
| 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. Popośniakowe hiperglikemie po posiłkach o wysokim indeksie glikemicznym.

Fig. 2. The mean HbA1c in subject treated 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.
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 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 al. 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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