RENAL ASSESSMENT IN TEENAGE PATIENTS WITH CYSTIC FIBROSIS – PRELIMINARY REPORT

OCENA FUNKCJI NEREK U NASTOLatków Z MUKOWISCYDOZĄ – DONIESIENIE WSTĘPNE

Abstract

**Background:** Together with increasing life expectancy of patients with cystic fibrosis (CF), there is a growing need to deal with unforeseen problems and complications. Among others renal dysfunction has become of great concern.

**Aim:** Evaluation of renal function in CF children.

**Material and methods:** We performed cross-sectional study on a group of 11 teenage inpatients with CF. Physical examination, past medical history analysis, renal function measurements and analysis were conducted in all of them. Renal assessment included: serum cystatin C and creatinine levels, measured and estimated creatinine clearance, estimated cystatin C clearance, urine indicators of crystallization risk and renal ultrasonography.

**Results:** One patient had elevated serum cystatin C level and diminished McIsaac equation. Renal ultrasound revealed non-congenital anomaly in 1 case – it was nephrolithiasis. All the individuals had elevated at least 1 urine indicator of crystallization risk.

**Conclusion:** There is a great need of good, standardized test of renal function in cystic fibrosis patients. The focus of research should turn towards finding a tool similar to faecal elastase, which is cheap, easy to perform, sensitive and specific, and can be used to confirm the diagnosis.

**Key words:** renal function, CF

Streszczenie

**Wstęp:** Wraz z wzrastającą długością życia chorych na mukowiscydozę (CF), zaistniała potrzeba radzenia sobie z nowymi jej powikłaniami. Między innymi zaburzenie czynności nerek stało się nowym wyzwaniem.

**Cel:** Ocena czynności nerek u dzieci z mukowiscydozą.

**Materiał i metody:** Przeprowadzono badanie przekrojowe na grupie jedenastu nastoletnich pacjentów z CF hospitalizowanych w IMiDz. U wszystkich przeprowadzono dokładny wywiad dotyczący przebiegu choroby, wywiad rodzinny, badanie fizyczne oraz pomiary czynności nerek. Ocena nerek polegała na oznaczeniu: cystatyny C i kreatyniny w surowicy, klirensu kreatynyny oraz klirensu cystatyny C, wskaźników ryzyka krystalizacji moczu i USG nerek.

** Wyniki:** Jeden pacjent miał podwyższone stężenie cystatyny C w surowicy oraz obniżony klirens cystatyny McIsaac. W 1 przypadku USG nerek wykazało nieprawidłowość – była to kamica nerkowa. U wszystkich badanych pacjentów co najmniej jeden wskaźnik ryzyka krystalizacji moczu był podwyższony.

**Wnioski:** Istnieje wielka potrzeba dobrego, wystandaryzowanego badania czynności nerek u pacjentów z mukowiscydozą. Przedmiotem badań powinno być znalezienie narzędzia podobnego do oznaczenia stężenia elastazy w kolec – testu, który jest łatwy do wykonania, czytu i specyficzny oraz może być stosowany w celu potwierdzenia diagnozy.

**Słowa kluczowe:** funkcja nerek, mukowiscydoza
INTRODUCTION

Life expectancy of patients with cystic fibrosis increased approximately 8-fold during half a century – whereas in 1950s most patients died before the age of 5 years, nowadays the median survival is over 41 years [1], and is expected to be longer [2]. This great achievement of medicine has been possible due to enormous technical and scientific progress: new methods of screening newborns and extended genetic analysis of cystic fibrosis transmembrane conductance regulator (CFTR) gene, enabling early diagnosis prevention of early complications and changing natural course of the disease), availability of new possibilities in treatment, methods enabling enteral feeding (which partially solved problems of malnutrition), advances in physiotherapy (improvement of sputum clearance and thus reducing respiratory tract infections rate), more aggressive antibiotic and antifungal treatment of lung infections caused by opportunistic pathogens such as Pseudomonas aeruginosa and Aspergillus fumigatus, and better treatment of respiratory failure including home oxygen therapy and lung transplantation [3].

In conjunction with a great improvement in holistic care of cystic fibrosis patients, medical workers dealing with the disease have to face numerous unforeseen problems. Complications associated with extended life expectancy include: lung colonization and infections with multi-resistant pathogens, diabetes, osteoporosis, gastroesophageal reflux and liver diseases together with their complications (for example, esophageal varices) [3]. Novel approaches have been developed to minimize respiratory and gastrointestinal complications both in pediatric and adult patients. Currently, there is an increasing concern in renal complications. However, there was no consensus on the best method assessing renal function in CF.

Cystic fibrosis transmembrane conductance regulator (CFTR) is found in kidneys (mainly in the proximal and distal tubules) and its inactivation can cause proteinuria – as it was shown in mice models [4]. What is interesting, microscopic nephrocalcinosis has been found in 90% human autopsies, including those done near the time of birth, which suggests that such renal calcium deposits reflect rather genomic defect [5]. However its exact role in CF related kidney disease remains unknown and primary kidney disease is unusual, whereas secondary renal dysfunction is becoming increasingly common in teenage and adult patients. Natural age-dependent gradual reduction in number of nephrons is known to be accelerated by chronic infection (including colonization with Pseudomonas aeruginosa), vascular changes and diabetes, which all can occur in the course of CF [1]. Moreover, CF individuals are at risk of both chronic renal disease and acute kidney injury through exposure to potentially nephrotoxic drugs. Such pharmacological agents include: non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, ciprofloxacin, colistin, azithromycin, cepazidime, proton pomp inhibitors (PPI), sulphonamides, rifampicin, diuretics and immunosuppressants. Together with longer life expectancy, lifetime exposure to those drugs increases. Further renal pathologies concerning CF patient population include: nephrolithiasis, amyloidosis and IgA nephropathy. The incidence of nephrolithiasis in CF patients is about 6%, and is approximately 3-fold higher than in their age-matched healthy controls [6]. The mechanisms responsible for this phenomenon are: low urine volume associated with salt depletion and dehydration, prolonged episodes of immobilization, hyperoxaluria, hyperuricosuria and hypercalciuria [1]. Amyloidosis is increasingly being recognized in CF, as it is inflammation-associated complication of chronic infections [7]. Chronic inflammation and recurrent infections can also result in high levels of IgA and thus cause IgA nephropathy. In addition, the presence of liver disorders in CF, impairs immune complex clearance and increases renal deposition [1, 8].

Currently, the standard assessment of renal function is limited to renal blood flow and glomerular filtration rate (GFR), which is estimated and measured with proteinuria and filtration markers clearance derived from various formulae [1]. Although GFR is the most commonly accepted parameter that reflects renal function, it has its limitations. So called gold standard tests (using isotopic and non-isotopic clearance rates, i.e.: Cr-EDTA, I-labeled iothalamate, iohexol, inulin, mTc-DTPA) are invasive, costly, time-consuming and non available for routine use. Creatinine clearance measured on basis of 24 h urine collection is time-consuming and depended on accuracy of the procedure. Whereas creatinine clearance estimated using equations are based mainly on plasma creatinine, which is depended on tubular secretion of creatinine and affected by age, sex, weight, physical activity and certain drugs. Al-Aloul et al compared 10 equations with control, which was 24 h urine collection and concluded that none of these methodologies could be used reliably to assess renal function in patients with CF [9]. Theoretically an ideal endogenous marker for estimating GFR is serum cystatin C, as it is mainly determined by glomerular filtration and is not affected by muscle mass, sex or age [3]. Beringer et al showed superiority of this marker to creatinine-based equations in patients with CF [10]. MacIsaac et al suggested usefulness of screening chronic kidney disease in subjects with diabetes by simple measuring serum cystatin C levels [11]. In contrast, Soulsby et al, who compared different renal function measurement methods in adult and children with CF, did not found significant differences between creatinine and cystatin C based equations [12].

As GFR is also insensitive in detection of early renal dysfunction (up to 30% of nephrons can cease to function before GFR alters), there is interest in finding less invasive and time-consuming, and more reliable marker to monitor renal function. Such sensitive tools, which can potentially be useful in the early diagnosis of renal injury, are urinary enzymes: N-acetyl-β-D-glucosaminidase (NAG) and alanine amino-peptidase (AAP). They are related to acute kidney injury (AKI). Elevated excretion of these markers were reported in connection with intravenous aminoglicoside and tobramycin therapy.
in patients with CF [13, 14]. There are also other markers considered to be indicators of acute kidney insult – neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1), but first of them appears to be useless in CF as it is also produced in response to epithelium damage in the lungs [1]. It should be stressed, that all these biomarkers are relevant for current identification of early iatrogenic tubular injury and cannot be used for drugs dose adjustments or stratification of risk of urine supersaturation with renal stones promoters. This remains to be the domain of methodologies related to evaluation of glomerular filtration, nevertheless their poor sensitivity in terms of early detection of acute kidney injury (AKI).

AIM

The aim of the study was to evaluate renal function in CF children.

PATIENTS AND METHODS

Study population

Eleven consecutive CF inpatients chronically infected by Pseudomonas aeruginosa, who were admitted to the hospital due to exacerbation of broncho-pulmonary changes, formed the study population mean age 14.9 (SD 1.08, range 13-17) – see Table I. A patient’s median Shwachman–Kulczycki score was 74.5 (SD 10.54, range 60-90). One patient had an additional nephrologic problem defined as chronic haematuria, one was diagnosed with CF-related diabetes mellitus, one had nephrolithiasis and one had congenital malformation of kidney and ureter. The remaining did not have previous history of renal problems, including acute drug-related kidney injury. Five children were partially enterally fed with percutaneous endoscopic gastrostomy (PEG) because of very low body mass index (BMI). All except one had a vitamin D deficiency. During the study all the patients were treated with potentially nephrotoxic intravenous antibiotics (aminoglycosides administered once daily or colistin), five of them required oral proton pump inhibitor and three of them were during oral antifungal treatment (itraconazole). We could not exclude the possibility of taking other potentially nephrotoxic drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), azithromycin or sulphonamides in the past. No patient had undergone transplantation or was taking immunosuppressive therapy (which could cause renal disease). None of the teenagers presented with clinical symptoms of renal disease. None of them had positive family history of renal problems.

Table I. Patients’ characteristics.

Tabela I. Charakterystyka pacjentów.

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age (years)</th>
<th>Body mass (kg)</th>
<th>Body mass index (BMI)</th>
<th>Shwachman-Kulczycki score</th>
<th>PEG</th>
<th>CFRD</th>
<th>Urinary system pathology in USG</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Pacjent</td>
<td>Wiek (lata)</td>
<td>Masa ciała</td>
<td>Wskaźnik masy ciała</td>
<td>Skala Shwachmana-Kulczyckiego</td>
<td></td>
<td></td>
<td>Patologia w badaniu USG</td>
</tr>
<tr>
<td>1.</td>
<td>14</td>
<td>48.5</td>
<td>18.5</td>
<td>85</td>
<td>no</td>
<td>no</td>
<td>niewykluczalna malformacja</td>
</tr>
<tr>
<td>2.</td>
<td>14</td>
<td>53.5</td>
<td>23.7</td>
<td>75</td>
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<td>no</td>
<td>niewykluczalna malformacja</td>
</tr>
<tr>
<td>3.</td>
<td>16</td>
<td>52.5</td>
<td>17.7</td>
<td>85</td>
<td>no</td>
<td>no</td>
<td>niewykluczalna malformacja</td>
</tr>
<tr>
<td>4.</td>
<td>16</td>
<td>44.5</td>
<td>17.6</td>
<td>80</td>
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<td>no</td>
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</tr>
<tr>
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<td>15</td>
<td>37</td>
<td>13.9</td>
<td>65</td>
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<td>6.</td>
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</tr>
<tr>
<td>7.</td>
<td>14</td>
<td>37.8</td>
<td>15.3</td>
<td>60</td>
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<td>no</td>
<td>uréra zrubiona woda nerek</td>
</tr>
<tr>
<td>8.</td>
<td>17</td>
<td>61.8</td>
<td>19.5</td>
<td>85</td>
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<td>no</td>
<td>niewykluczalna malformacja</td>
</tr>
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<td>9.</td>
<td>15</td>
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<td>21</td>
<td>90</td>
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</tr>
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<td>18</td>
<td>65</td>
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<td>no</td>
<td>niewykluczalna malformacja</td>
</tr>
<tr>
<td>11.</td>
<td>15</td>
<td>26</td>
<td>14.7</td>
<td>60</td>
<td>yes</td>
<td>no</td>
<td>niewykluczalna malformacja</td>
</tr>
</tbody>
</table>

PEG – percutaneous endoscopic gastrostomy (przeczkórná endoskopowa gastrostomia), CFRD – Cystic Fibrosis Related Diabetes (kureksza związana z Mukowickeydą), USG – ultrasonography (ultrasonografia).
Assessment of renal function

**Serum and urine creatinine**

Serum and urine creatinine were measured according to the Jaffe method using Roche Integra 400 plus analyser. The normal range for serum creatinine in our laboratory is 50-120 μmol/l.

**Plasma Cystatin C**

Plasma Cystatin C was measured by an optimized immunoturbidimetric method.

**Measured creatinine clearance**

This was assessed in every patient by comparing urinary creatinine (UCr) cleared over 24 hours with the serum creatinine (SCr) obtained at the beginning of hospitalization. Serum and urine creatinine were measured according to the Jaffe method using Roche Integra 400 plus analyser. The clearance of endogenous creatinine was determined by the formula mCCL = (UCr×urine volume)/SCr and expressed as ml/min adjusted for body surface area index (1.73/body surface area).

The normal range for serum creatinine in our laboratory is 50-120 μmol/l. It must be stated, that these values are not age-related normal range. [15] The minimum value for normal creatinine clearance in our laboratory is set at 80 ml/min/1.73 m².

**Estimated GFR (glomerular filtration rate)**

1. Estimated creatinine clearance
   - This was calculated according to the Schwartz equation [16], where serum creatinine is adjusted for age, sex and body height to estimate creatinine clearance and thus GFR.
   - eGFR (ml/min/1.73 m²) = (height×0.413)/SCr in mg/dl.

2. Estimated cystatin C clearance
   - This was calculated according to the McIsaac equation [11]:
   - eGFR = (87/cystatin C [mg/l])-4.2.
   - Normal range of eGFR is >90 ml/min/1.73 m².

**Proteinuria**

The urine protein concentration was measured by quantitative Ektxon method.

**Renal ultrasonography**

An ultrasound imaging was performed by experienced pediatric radiologists in our hospital.

Urine indicators of crystallization risk:

- Hypercalciuria – in 24 h urine collection by colorimetric determination; was defined as >4 mg Ca/kg/24h urinary excretion,
- Ca/cr (calcium/creatinine) ratio – calculated basing on measurements in 24 h urine collection, elevated when >0.21 mg/mg,
- Hyperphosphaturia – 24 h urine collection by phosphorus molybdenum method; was defined as >20 mg phosphates/kg/24 h urinary excretion,
- TRP (tubular reabsorption of phosphates) – calculated basing on measurements in 24 h urine collection, normal range 85-95%,
- Hyperuricuria – in 24 h urine collection by enzymatic assay; was defined as >10 mg uric acid/kg/24 h urinary excretion,
- UA/Cr (uric acid/creatinine) ratio – counted basing on measurements in 24 h urine collection, elevated when >0.6 mg/mg,
- Magnesium excretion – in 24 h urine collection by colorimetric determination; normal range was defined as >1.8 mg Mg/kg/24 h urinary excretion,
- Mg/Ca ratio – normal range 0.8-1.3 [mg/mg].

**RESULTS**

**Renal function**

Only one patient had slightly impaired renal function, when assessed by cystatin C-based estimation – his cystatin C serum concentration was elevated and his eGFR according to McIsaac equation was diminished (see Table II, patient No 10). However his eGFR according to Schwartz equation was within normal ranges, his measured creatinine clearance and his serum creatinine concentration was slightly diminished – like in all the remaining subjects (which is probably connected with low muscular mass of our patients). In 9 patients cystatin C and McIsaac equation were within normal ranges, and in 1 patient this parameter was not measured.

None of the individuals presented with proteinuria.

**Renal ultrasonography**

An ultrasound imaging revealed abnormalities in 2 cases: 1 patient had bilateral nephrolithiasis and 1 had congenital kidney and ureter malformation. In the first subject nephrolithiasis was connected with haematuria, hyperphosphaturia, hyperuricuria and elevated uric acid/creatinine ratio. In the second subject there were elevated Ca/creatinine ratio, hypomagnesuria and diminished Mg/Ca ratio. Renal function (assessed using above described methods) was normal in both cases.

**Urine indicators of crystallization risk**

Serum concentrations of calcium, phosphates, magnesium and uric acid were within normal ranges in all the patients. All the subjects had elevated at least 1 urine indicator of crystallization risk (see Table III):

- Hypercalciuria was found in 6 individuals, among whom 5 had elevated calcium/creatinine ratio. 2 patients with normocalciuria presented with elevated calcium/creatinine ratio.
- Hypuricuria was found in 6 patients. In 5 cases it was correlated with elevated uric acid/creatinine ratio, in 3 cases with both hypercalciuria and hyperphosphaturia, in 1 case with hyperuricuri alone, and in 1 case with hyperphosphaturia alone.
- Hyperphosphaturia was identified in 4 subjects.
- TRP (tubular reabsorption of phosphates) was within normal ranges in all the individuals.
- Diminished magnesium excretion was found in 4 cases and diminished Mg/Ca ratio in 6.

The only patient with CF-related diabetes mellitus had hypercalciuria, elevated Ca/crea ratio, hyperuricuria,
Table II. Serum creatinine and cystatin C concentrations, and estimated GFR according to Schwartz and McIsaac equations.

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Serum creatinin (mg/dL)</th>
<th>Cystatin C (mg/L)</th>
<th>Schwartz equation</th>
<th>MacIsaac equation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stężenie kreatyniny</td>
<td>Cystatyna C</td>
<td>Formuła Schwartza</td>
<td>Formuła McIsaacca</td>
</tr>
<tr>
<td>1</td>
<td>0.44</td>
<td>0.74</td>
<td>152</td>
<td>113</td>
</tr>
<tr>
<td>2</td>
<td>0.40</td>
<td>0.87</td>
<td>155</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>0.55</td>
<td>0.87</td>
<td>129</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>0.34</td>
<td>0.84</td>
<td>193</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>0.45</td>
<td>0.82</td>
<td>150</td>
<td>102</td>
</tr>
<tr>
<td>6</td>
<td>0.45</td>
<td>0.70</td>
<td>155</td>
<td>120</td>
</tr>
<tr>
<td>7</td>
<td>0.31</td>
<td>0.86</td>
<td>209</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>0.44</td>
<td>0.74</td>
<td>167</td>
<td>113</td>
</tr>
<tr>
<td>9</td>
<td>0.55</td>
<td>0.79</td>
<td>129</td>
<td>106</td>
</tr>
<tr>
<td>10</td>
<td>0.48</td>
<td>1.03</td>
<td>149</td>
<td>80</td>
</tr>
<tr>
<td>11</td>
<td>0.42</td>
<td>-</td>
<td>131</td>
<td>-</td>
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</table>

Table III. Urine indicators of crystallization risk in the study group.

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Ca excretion (mg/kg/24h)</th>
<th>Ca/cr ratio (mg/mg)</th>
<th>UA excretion (mg/kg/24h)</th>
<th>UA/cr ratio (mg/mg)</th>
<th>Mg excretion (mg/kg/24h)</th>
<th>Mg/Ca ratio (mg/mg)</th>
<th>P excretion (mg/kg/24h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wydalenie wapnia</td>
<td>Współczynnik Ca/Kr</td>
<td>Wydalenie kwasu moczowego</td>
<td>Współczynnik UA/Kr</td>
<td>Wydalenie magnezu</td>
<td>Współczynnik Mg/Ca</td>
<td>Wydalenie fosforu</td>
</tr>
<tr>
<td>1</td>
<td>7.69</td>
<td>0.31</td>
<td>13.33</td>
<td>0.54</td>
<td>3.36</td>
<td>0.726</td>
<td>22.4</td>
</tr>
<tr>
<td>2</td>
<td>0.38</td>
<td>0.04</td>
<td>7.90</td>
<td>0.83</td>
<td>0.95</td>
<td>4.194</td>
<td>7.9</td>
</tr>
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<td>0.17</td>
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<td>1.82</td>
<td>0.697</td>
<td>15.6</td>
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<td>7.73</td>
<td>0.37</td>
<td>13.32</td>
<td>0.64</td>
<td>2.98</td>
<td>0.640</td>
<td>29.1</td>
</tr>
<tr>
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<td>6.27</td>
<td>0.26</td>
<td>19.21</td>
<td>0.81</td>
<td>1.51</td>
<td>0.399</td>
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<tr>
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<td>3.87</td>
<td>0.25</td>
<td>7.67</td>
<td>0.49</td>
<td>1.66</td>
<td>0.712</td>
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</tr>
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<td>0.39</td>
<td>17.63</td>
<td>0.89</td>
<td>3.93</td>
<td>0.829</td>
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<td>3.22</td>
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<td>17.52</td>
<td>0.63</td>
<td>2.59</td>
<td>1.331</td>
<td>25.3</td>
</tr>
<tr>
<td>9</td>
<td>2.41</td>
<td>0.22</td>
<td>5.30</td>
<td>0.48</td>
<td>1.27</td>
<td>0.876</td>
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<td>0.20</td>
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<td>2.01</td>
<td>0.833</td>
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</tr>
<tr>
<td>11</td>
<td>6.15</td>
<td>0.36</td>
<td>9.64</td>
<td>0.59</td>
<td>2.75</td>
<td>0.739</td>
<td>18.78</td>
</tr>
</tbody>
</table>

Ca – calcium (wapń), Ca/Cr ratio – calcium/creatinine ratio (współczynnik wapń/kreatynina), UA – uric acid (kwas moczowy), UA/Cr ratio – uric acid/creatinine ratio (współczynnik kwas moczowy/kreatynina), Mg – magnesium (magnez), Mg/Ca ratio – magnesium/calcium ratio (współczynnik magnez/wapń), P – phosphate (fosfor).
Table IV. Comparison of contribution of patients with improper urine indicators of crystallization risk in groups with and without PEG.

<table>
<thead>
<tr>
<th></th>
<th>Hypercalciumia (Hiperkalcemia)</th>
<th>↑Ca/Cr Podwyższony wskaźnik Ca/Kr</th>
<th>Hyperuricemia (Hiperurykozemia)</th>
<th>↑UA/Cr Podwyższony wskaźnik UA/Kr</th>
<th>↓Mg/Ca Obniżony wskaźnik Mg/Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>with PEG (żywienie dojelitowe)</td>
<td>4/4</td>
<td>4/4</td>
<td>3/4</td>
<td>3/4</td>
<td>2/4</td>
</tr>
<tr>
<td>without PEG (bez żywienia dojelitowego)</td>
<td>2/7</td>
<td>3/7</td>
<td>3/7</td>
<td>3/7</td>
<td>3/7</td>
</tr>
</tbody>
</table>

elevated UA/crea ratio, diminished magnesium excretion and Mg/Ca ratio, but hypophosphaturia.

We observed the tendency to more often presence of improper indicators of crystallization risk among patients with PEG. In comparison to the patients without PEG the contribution of cases with improper crystallization indicators was higher – see Table IV. All PEG patients were treated with oral proton pump inhibitor (PPI). From the group without PEG, 2 subjects were given PPI. Both of them had elevated Ca/Cr ratio, hypercalcemia and diminished Mg/Ca ratio, one had hyperuricemia and elevated UA/Cr ratio.

**DISCUSSION**

The group is too small to perform any statistical analysis and to draw any binding conclusions. The blood samples were taken and the urine collections were conducted in artificial circumstances, i.e. during hospitalization due to exacerbation of broncho-pulmonary changes. Thus it was connected with respiratory effort, metabolism changed by infection status, diminished activity, partially changed diet. All the patients were given potentially nephrotoxic antibiotics intravenously at the moment of performing measurements, which could also influence the results, although we disposed only routine test, so novel indicators of AKI were not checked.

We found slightly diminished renal function only in 1 patient and even this estimated using only 1 method (according to the other it was proper). Yet risk of nephrocalcinosis and nephrolithiasis seemed to be increased in all of the cases – every individual had elevated at least one urine indicator of crystallization risk. There was a tendency for further increase in patients with PEG. It raises the question about the influence of enteral nutrition formulas on these indicators. High protein diet and purine-rich pancreatic enzyme supplementation are the risk factors for hyperuricaemia. Hypercalcemia may be secondarily caused by increased tubular phosphate and sodium loss, present in proximal renal tubules in these patients. Drug-related tubular toxicity may be one of the reasons of increased phosphaturia. The second reason might be secondary hyperparathyroidism due to vitamin D deficit, unfortunately it was not assessed in presented patients [17].

We did not measure oxaluria and citruria which are also reputed to play role in nephrolithiasis [18, 19]. It should be stressed, that reported incidence of hyperoxaluria and hypocitruria are significantly (three-times) bigger, than hypercalcemia and hyperuricemia in cystic fibrosis patients, so further evaluation in this term would be valuable.

Some researchers suggest, that not markers themselves, but their changes in time may be of bigger value. This, of course, demands prospective, time-consuming study.

**CONCLUSION**

 Routinely available tests assessing renal function are not unsophisticated, sensitive and reliable enough to properly monitor cystic fibrosis patient population for onset of renal dysfunction. However, the problem is not restricted to this specific group of patients, the whole nephrology world is awaiting for such (an) indicator(s). The problem demands non only further prospective studies on bigger groups of patients, but also basic in vitro and animal studies. From a "CF point of view", the focus of research should turn towards finding a tool similar to faecal elastase, which is cheap, easy to perform, sensitive and specific, and can be used both to confirm diagnosis and to monitor disease progression.

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Conflicts of interest/Konflikt interesu
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