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COMPARISON OF 72-HOUR FECAL FAT QUANTIFICATION AND THE ^{13}C-MIXED TRIGLYCERIDE BREATH TEST IN ASSESSING PANCREATIC EXOCRINE SUFFICIENCY IN CHILDREN WITH CHRONIC PANCREATITIS

PORÓWNANIE PRZYDATNOŚCI BILANSU TŁUSZCZOWEGO W 3-DOBOWEJ ZBIÓRCE KAŁU I TESTU ODDECHOWEGO Z TRIGLICERYDAMI ZNAKOWANYMI WĘGLEM ^{13}C W OCENIE WYDOLNOŚCI ZEWNĄTRZWYDZIELNICZEJ TRZUSTKI U DZIECI Z PRZEWLEKŁYM ZAPALENIEM TRZUSTKI

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Abstract

Introduction: *Chronic pancreatitis (CP) in children is still a rare, although increasingly recognized entity. Over the duration of the disease several complications can be observed, two of which are major ones: endo- and exocrine insufficiency. In the medical care of children with CP it is crucial to diagnose the decreased endo- and exocrine function of the pancreas, in order to preserve patients from malnutrition and the failure to thrive. The aim of the study was to compare the usefulness of two indirect methods of assessing the pancreas exocrine function in children with CP.*

Material and methods: *Ninety one patients with CP were enrolled in the study (41 boys, 50 girls, aged 2-17.8 years). Only Patients who had had both the 72-hour fecal fat quantification and the ^{13}C-mixed triglyceride breath test (^{13}C -MTBT) performed were selected. We compared the results of both tests for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in detecting exocrine pancreatic insufficiency.*

Results: *Out of 91 patients, 12 were diagnosed with exocrine pancreatic insufficiency (EPI). The sensitivity of the fecal fat quantification was 50%, the specificity for the test was 100%. PPV and NPV were 100% and 93%, respectively. ^{13}C-MTBT had the sensitivity of 42% and the specificity of 99%. PPV and NPV for the breath test were of 83% and 92%, respectively. No statistically significant discrepancy between the values obtained was found.*

Conclusions: *Although the 72-hour fecal fat quantification remains the gold standard in detecting EPI, both of the methods that had been investigated were shown to be comparable regarding sensitivity, specificity, PPV and NPV in assessing pancreas exocrine sufficiency in children with CP. Due to the easier execution of the breath test, both for the patient and for medical personnel, its importance may increase.*

Key words: chronic pancreatits, children, pancreatic exocrine insufficiency, breath test, fecal fat quantification

Streszczenie

Wstęp: *Przewlekłe zapalenie trzustki (PZT) u dzieci jest nadal chorobą rzadką, choć jej rozpoznawalność wzrasta na całym świecie. Wraz z czasem trwania choroby mogą być obserwowane jej liczne*

powikłania, m.in. niewydolność zewnątrz- oraz wewnątrzwydzielnicza trzustki. W opiece nad pacjentami z PZT istotna jest regularna ocena funkcji narządu, by zapobiec następstwom powikłań, takim jak niedożywienie czy opóźnione wzrastanie i rozwój. Celem naszej pracy było porównanie użyteczności dwóch metod oceny zewnątrzwydzielniczej funkcji trzustki.

Materiał i metody: *Do badania włączono 91 pacjentów z PZT (41 chłopców, 50 dziewczynek w wieku 2-17,8 lat). Do analizy zakwalifikowani zostali jedynie pacjenci, którzy mieli wykonane oba testy, zarówno bilans tłuszczowy w 3-dobowej zbiórce kału, jak i test oddechowy ze znakowanymi węglem ^{13}C triglicerydami.*

Wyniki: *Spośród 91 pacjentów włączonych do badania, u 12 zdiagnozowano niewydolność zewnątrzwydzielniczą trzustki. Czułość bilansu tłuszczów w 3-dobowej zbiórce kału wyniosła 50%, swoistość 100%. Wartość predykcyjna dodatnia (PPV) i wartość predykcyjna ujemna (NPV) wyniosły odpowiednio 100% i 93%. Test oddechowy z triglicerydami znakowanymi izotopem węgla ^{13}C wykazał się czułością 42% i swoistością 99%. PPV i NPV wyniosły 83% i 92%. Różnice w otrzymanych wynikach nie osiągnęły progu istotności statystycznej.*

Wnioski: *Bilans tłuszczów w 3-dobowej zbiórce kału pozostaje nadal złotym standardem w diagnostyce niewydolności zewnątrzwydzielniczej trzustki, jednak obie porównywane metody diagnostyczne wykazały podobną czułość, swoistość, PPV oraz NPV. Wobec łatwiejszego, zarówno dla pacjenta, jak i dla personelu medycznego, wykonania testu, znaczenie testu oddechowego z triglicerydami ze znakowanym węglem ^{13}C może w przyszłości wzrastać.*

Słowa kluczowe: przewlekłe zapalenie trzustki, dzieci, niewydolność zewnątrzwydzielnicza trzustki, test oddechowy, bilans tłuszczowy w kale

INTRODUCTION

Chronic pancreatitis (CP) is a rare disease in children, however its prevalence is continuously increasing all over the world. The essence of the disease is the destruction of the organ's parenchyma by a progressive inflammation process, and its gradual replacement with connective tissue, and thus the progressive impairment of pancreatic functions [1].

The major causes of CP in children differ significantly from those described among adults and the most important ones include gene mutations (i.e. *SPINK1, CFTR, PRSS1, CTRC, CPA1*), anatomical defects of the pancreatic duct, lipid disorders and diseases of the biliary tract [2-6]. Despite the dynamic development of imaging and molecular diagnostic methods, up to 30-40% of CP remains idiopathic [3].

Chronic pancreatitis is associated with numerous short- and long-term complications. The latter are mainly exocrine and endocrine insufficiency. Due to the large functional reserves of the pancreas, exocrine and endocrine insufficiency occurs after about 90% of the gland's parenchyma is destroyed by the inflammation process [7]. Thus, long-term complications are observed after many years of the disease's duration and they are mostly diagnosed in adult patients. It is crucial to assess exocrine and endocrine sufficiency regularly, to provide proper medical management to a patient with CP and prevent the severe consequences of the disease. To monitor the development of diabetes the simple test of fasting glucose or plasma glucose after glucose intake is used [8]. The exocrine pancreatic insufficiency (EPI) diagnosis can

be made on the basis of several function tests, including fecal fat quantification (considered as the gold diagnostic standard for steatorrhea), fecal elastase-1 (FE-1) and the ^{13}C-mixed triglyceride breath test (^{13}C-MTBT) [9].

AIM

The comparison of the usefulness of the 72-hour fecal fat quantification and the ^{13}C-Mixed Triglyceride Breath Test in assessing exocrine pancreatic insufficiency in children with CP was the aim of our study.

MATERIAL AND METHODS

Ninety one patients with CP hospitalized in the Department of Gastroenterology, Hepatology, Feeding Disorders and Pediatrics, the Children's Memorial Health Institute, between the years 1988 and 2015 were enrolled in the study (41 boys, 50 girls, aged 2-17.8 years). Patients who had had both the 72-hour fecal fat quantification and the ^{13}C-mixed triglyceride test performed were selected.

The diagnosis of CP was established according to the INSPIRE recommendation – where 1 of 3 criteria were to be met: 1) abdominal pain consistent with pancreatic origin and imaging findings suggestive of chronic pancreatic damage, 2) evidence of exocrine pancreatic insufficiency and suggestive pancreatic imaging findings or 3) evidence of endocrine pancreatic insufficiency and suggestive pancreatic imaging findings. The suggestive pancreatic findings included ductal changes (irregular contour of the main pancreatic duct or its radicles, intraducting

filling defects, calculi, stricture or dilatation) as well as parenchymal ones (generalized or focal enlargement, irregular contour cavities, calcifications, heterogeneous echotexture) [8]. Imaging modalities included the US scan, CT, MRI, MRCP and ERCP.

For the fecal fat quantification using the modified van de Kamer method, samples were pooled over a 3-day period while consuming a normal patient's diet. The enzyme replacement therapy, if being implemented, was withheld 7 days before stool collection. In patients who had undertaken more than one test, the highest result was taken into consideration. Fecal fat quantities of >5 g/day were considered to be abnormal.

The ^{13}C-mixed triglyceride breath test was performed on the IRIS® Infra Red Isotope Analyzer. After 10 hours of fasting, the patient was given a meal consisting of 15mg ^{13}C-Mixed Triglycerides per kilogram <30 kg of weight or 5 mg ^{13}C-Mixed Triglycerides per kilogram >30 kg of weight with 0.25 g of butter per kilogram body weight and 100g of bread. Breath samples were collected before (2x) and every 30 minutes for 360 minutes (6 h) after the ingestion of the ^{13}C-Mixed Triglycerides. Each sample was collected in a separate bag. ^{13}C enrichment in breath CO_2 was determined using Isotope Ratio Mass Spectrometry (IRMS). The cumulative percentage of ^{13}C recovered in the breath during the 360 minute collection period is used as the diagnostic parameter. Values below 22% of the 6 hour cumulative recovery indicate diminished lipase activity.

The results of both tests for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in detecting exocrine pancreatic insufficiency were compared.

The chi-square test was used to compare relative frequencies, the significance was assumed at p < 0.05.

RESULTS

Out of 91 patients enrolled in the study, 12 were diagnosed with exocrine pancreatic insufficiency (5 boys, 7 girls) (tab. I).

Fecal fat quantification turned out to have had the sensitivity of 50% for the diagnosis of exocrine pancreatic insufficiency, while the specificity for the test was 100%. PPV (Positive Predictive Value) and NPV (Negative Predictive Value) were 100% and 93%, respectively. Patients with false negative results of fecal fat quantification were diagnosed with insufficiency using the fecal elastase-1 test (FE-1). The ^{13}C-mixed triglyceride breath test showed the sensitivity of 42% and the specificity of 99%. PPV and NPV for the breath test were 83% and 92%, respectively, for exocrine pancreatic insufficiency recognition (fig. 1).

There was no significant difference between the diagnostic methods that had been investigated in obtaining consistent (true positive and true negative) as well as incompatible (false positive and false negative) test results (see tab. II).

Among patients with exocrine pancreatic insufficiency, the enzyme replacement therapy was implemented in 8 patients (8/12; 67%), 4 of them were not given the therapy (4/12, 33%).

Table I. Characteristics of patients with exocrine pancreatic insufficiency.

Tabela I. Charakterystyka pacjentów z niewydolnością zewnątrzwydzielniczą trzustki.

Patient No *Numer pacjenta*	Sex *Płeć*	Age of CP onset (years) *Wiek zachorowania (lata)*	BMI *BMI*	CP etiological /risk factor *Czynnik etiologiczny ryzyka*	Enzyme replacement therapy *Enzymatyczna terapia substytucyjna*
1.	F	9.4	13.5	*SPINK1* N34S/-	No
2.	F	4.2	15.7	*SPINK1* N34S/- *Ansa pancreatica*	Yes
3.	M	2.0	13.9	Choledochal cyst	Yes
4.	F	4.2	15.1	Hyperlipoproteinemia type 4	No
5.	F	8.7	13.8	*PRSS1* R122C/-	Yes
6.	M	15.8	21.4	*PRSS1* E79K/-	No
7.	F	2.9	18.3	Ansa pancreatica	Yes
8.	M	3.2	14.5	Pancreas divisum	No
9.	F	2.7	14.6	*PRSS1* R122C/-	Yes
10.	M	15.6	16.4	Primary Sclerosing Cholangitis (PSC)	Yes
11.	M	10.4	14.1	-	Yes
12.	F	6.2	15.5	-	Yes

DISCUSSION

Exocrine pancreatic insufficiency (EPI) is defined as reduced pancreatic enzyme and bicarbonate secretion, or both, which results in the malabsorption of nutrients
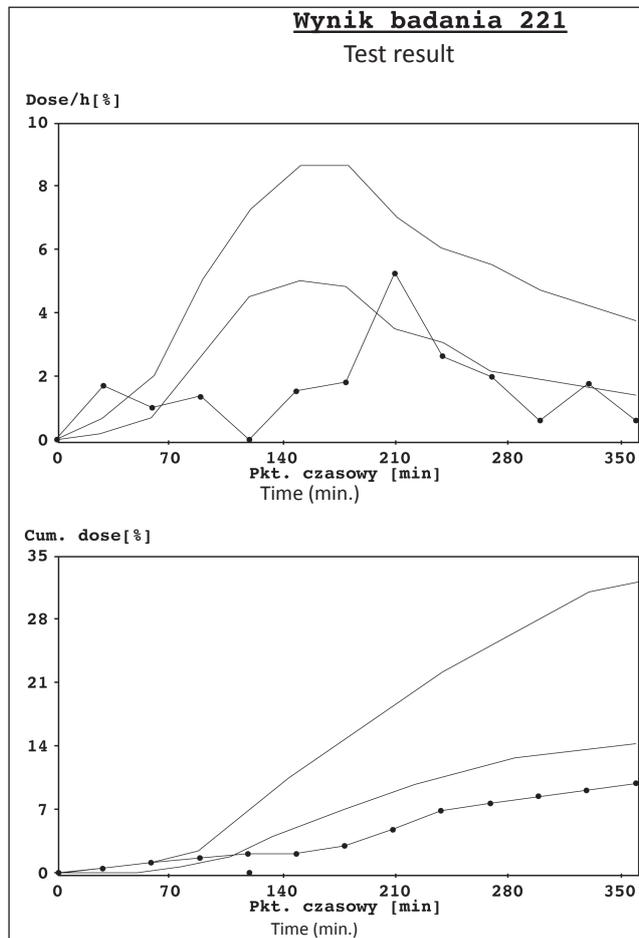

Fig. 1. ^{13}C-MTBT result indicating EPI.

[9]. If untreated, EPI results in steatorrhea, abdominal distension and discomfort, eventually malnutrition and failure to thrive in children. The treatment of EPI consists in administering the pancreatic enzyme replacement therapy, which reduces malabsorption and makes it possible to maintain proper nutrition [10]. To detect improper exocrine pancreatic secretion, and to control the efficacy of the EPI treatment, direct and indirect methods can be used. Direct methods are based on the assessment of stimulated pancreatic secretion and they allow to measure the actual enzyme activity (e.g. endoscopic test, pancreatic stimulation test [dreiling tube test], secretin-pancreozymin test or S-MPR [secretin-enhanced magnetic resonance pancreatography]). Direct tests are accurate and make it possible to detect even early stages of insufficiency, however their usefulness is limited by two major disadvantages: invasiveness and poor availability. Indirect methods are more widely used due to their easier applicability, safety for the patient, lower costs and, what is important in long-term treatment, they can be performed repeatedly without a burden on the patient. These tests include stool tests (fecal fat quantification, fecal elastase-1 (FE-1), stool chymotrypsin) and breath tests (^{13}C-mixed triglyceride breath test). It is also possible to assess the pancreas' function indirectly by testing nutritional markers in serum (e.g. fat-soluble vitamins, total cholesterol) but they are mainly used to monitor the patient's condition and to prevent vitamin deficiency and malnutrition [9, 11, 12].

The 72-hour-Fecal fat quantification using the modified van de Kamer method remains the gold standard for diagnosing EPI with fat maldigestion [13]. In adult patients fecal fat testing is performed after 3 days of a standardized high-fat diet, in children it is acceptable not to implement high fat intake. Nevertheless, it has to be emphasized that the fecal fat quantification is not a specific test for

Table II. Statistical analysis of the obtained tests results.

Tabela II. Analiza statystyczna wyników.

	72h-Fecal Fat Quantification	^{13}C-Mixed Triglyceride Breath Test	p value
True positive results (n) *Wyniki prawdziwie dodatnie (n)*	6	5	p<0.05; NS
True negative results (n) *Wyniki prawdziwie ujemne (n)*	79	78	p<0.05; NS
False positive results (n) *Wyniki fałszywie dodatnie (n)*	0	1	p<0.05; NS
False negative results (n) *Wyniki fałszywie ujemne (n)*	6	7	p<0.05; NS
Sensitivity (%) *Czułość (%)*	50	42	p<0.05; NS
Specificity (%) *Swoistość (%)*	100	99	p<0.05; NS
Positive Predictive Value (PPV)(%) *Wartość predykcyjna dodatnia (%)*	100	83	p<0.05; NS
Negative Predictive Value (NPV)(%) *Wartość predykcyjna ujemna (%)*	93	92	p<0.05; NS

pancreatic insufficiency due to the many possible reasons for high-fat excretion e.g. increased gut transit, high fat intake, small bowel bacterial overgrowth, gut mucosal injury, Crohn disease and many others. What was proved by Di Magno, the fecal fat test is hardly of use in detecting the early stages of insufficiency, as the pancreatic lipase output has to fall below 10% to induce incorrect results of the test [7]. Another limitation of fat quantification in stool is its unpleasant performance and time-consuming execution, therefore it is often affected by inadequate patient compliance. Moreover, patients with pancreatic insufficiency often suffer from diarrhea, which makes the stool collection more difficult. It is also challenging for parents to make the stool collection complete and adequate when it comes to younger children [14].

As pancreatic sufficiency is one of the major concerns in cystic fibrosis (CF), many studies assessing the usefulness of pancreas function tests were conducted among CF patients. The research of Weintraub et al [15] involved 21 pancreatic sufficient CF patients (median age 11.1 years, range: 9 months – 40 years). The authors correlated the results of the 72-hour fecal fat excretion, expressed as a coefficient of fat absorption (CFA) with two other tests: fecal elastase-1 and serum immunoreactive trypsinogen (IRT) for sensitivity, specificity, and positive and negative predictive values. The sensitivity, specificity, and positive and negative predictive values of IRT versus CFA were: 0%, 88%, 0%, and 78%, and for fecal elastase-1 were 40%, 81%, 40%, and 81%, respectively. The study proved 72-hour fecal fat quantification to be still a gold standard in pancreatic sufficiency assessment, despite its many disadvantages. In our study the specificity of 72-hour fecal fat quantification was 100%, the sensitivity turned out to be poor (42%).

The ^{13}C-Mixed Triglyceride Breath Test was developed by Vantrappen et al [16]. It measures intestinal lipolysis, as intestinal triglyceride absorption requires prior hydrolysis by pancreatic lipase to free fatty acids and mono-acyl-glicerol. After digestion, absorption and oxidation, carbon dioxide labeled ^{13}C appears in the exhaled air. Like other indirect function tests, it is reliable in detecting severe pancreatic insufficiency, but is of little use in establishing mild to moderate pancreatic secretion disorders.

It was proved the breath test is particularly appropriate for estimating the effect of the enzyme replacement therapy, which was proven by Dominguez-Munoz et al. The authors compared the results of ^{13}C – MTBT obtained from 29 adult patients with maldigestion secondary to CP to the coefficient of fat absorption. The test results were comparable when assessing fat absorption before and during treatment, which justifies using the breath test as the more convenient and equally accurate one in monitoring the enzyme replacement therapy [17].

The usefulness of ^{13}C – MTBT was assessed by Keller et al [18]. The study was conducted on adult patients (mean age 28 years). The authors correlated the results of the ^{13}C-Mixed Triglyceride Breath Test with the direct secretin test (S-T). The breath test (performed with an increased lipid dose, 26g) turned out to be well correlated with the direct test for assessing lipase output, even if it was a moderate-grade decrease. The sensitivity of the breath test for the detection of decreased lipase output was 100%, the specificity was 92%, which significantly exceeds the results obtained in our study (42% and 99% respectively). Moreover, the authors stated that test-time extension does not result in the further improvement of results, however shortening of the sampling time by less than 6 hours caused decreased sensitivity and specificity. The authors hypothesized that the high obtained sensitivity and the specificity was due to the strict limitation of physical activity during collecting the samples. Patients in our study were instructed to remain seated during the test, but their actual activity was not monitored, therefore it is difficult to consider whether it caused our lower results. The issue of the influence of physical activity on test results remains controversial. There is some evidence that it affects the $^{13}CO_2$ response to the application of ^{13}C-Mixed Triglycerides [19], but to date, no study clarifies whether physical activity should be prohibited during the test. The correction of gastric emptying velocity turned out to be without significant impact on the sensitivity and specificity of ^{13}C-MTBT. The repeatability of ^{13}C-MTBT was taken under consideration by Herzog et al [20]. The study was conducted on 9 CF patients (mean age 11.9 years) and 10 healthy controls (mean age 10.7 years). All the contestants underwent ^{13}C-MTBT twice at a 2- to 4-week interval. The authors concluded that it is crucial for the test to be more reliable, to take into account the measurement of total resting CO_2 production (vCO_2), and even taking vCO_2 into account, the repeatability of ^{13}C-MTBT proved to be poor. Among our patients 5 underwent the breath test more than once, in four the result was repeatedly normal, one patient developed pancreatic insufficiency and his test result turned from correct to abnormal. The repeatability of the test in our study turned out to be satisfactory.

The clinical usefulness of ^{13}C-MTBT in assessing pancreatic exocrine function after pancreatic surgery and its correlation with fecal elastase-1 was investigated by Nakamura et al [21]. The study conducted on 112 adult patients after various surgical procedures for various pancreatic disorders. As for the correlation of clinical symptoms (steatorrhea) with pancreatic function test results, fecal elastase-1 turned out to be more sensitive than the breath test – sensitivity 90% and 69%, respectively. The result for specificity of the i tests investigated was the opposite – 52% for the fecal elastase-1 test and 93% for ^{13}C-MTBT. The authors also proved that the fecal elastase-1 test accuracy is limited by steatorrhea – the exclusion of 29 patients with steatorrhea during the test decreased the P value of the correlation between investigated methods significantly. This conclusion is consistent with earlier research [22].

CONCLUSIONS

Despite the many disadvantages of the 72-hour fecal fat quantification, it remains to be the diagnostic gold standard in assessing pancreas exocrine sufficiency. Several alternative tests for the assessment of fat malabsorption have been researched. However, because of their numerous limitations and poor accuracy, most of them failed to be

of clinical use. The ^{13}C-Mixed Triglyceride Breath Test is the most widely accepted alternative test. According to the results obtained in our study, the usefulness for assessing pancreatic sufficiency in children with CP for both the methods that had been investigated was comparable. Due to being acceptable for patients and the less time-consuming execution of ^{13}C-MTBT, as well as the test's diagnostic accuracy, its importance may increase.

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