ELSEVIER
Journal of Cystic Fibrosis 5 (2006) 253–255
Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Unresponsive or non-compliant steatorrhea in cystic fibrosis?

Aleksandra Lisowska [a], Barbara Kaminska [b], Marian Grzymislawski [c], Karl-Heinz Herzig [d], Jaroslaw Walkowiak [a,*]

[a] *Department of Gastroenterology and Metabolism, Poznan University of Medical Sciences, Szpitalna 27/33, 60-572 Poznan, Poland*
[b] *Department of Gastroenterology and Oncology, Medical University in Gdansk, Nowe Ogrody 1-6, 80-803 Gdansk, Poland*
[c] *Department of Gastroenterology and Human Nutrition, Poznan University of Medical Sciences, Przybyszewskiego 49, 60-355 Poznan, Poland*
[d] *A.I. Virtanen Institute for Molecular Sciences, and Dept. of Internal Medicine, KYS, University of Kuopio, PO Box 1627, Neulaniementie 2, 70211 Kuopio, Finland*

Received 23 December 2005; received in revised form 7 May 2006; accepted 7 May 2006
Available online 9 June 2006

Abstract

In 105 pancreatic insufficient CF patients (steatorrhea and low fecal elastase-1 concentrations), the effectiveness of pancreatic enzyme therapy (PET) has been assessed (fecal fat losses and coefficient of fat reabsorption). Eight unresponsive subjects were checked for PET compliance with fecal chymotrypsin assay. Three patients were documented to be non-compliant. Unresponsive patients should undergo evaluation for PET compliance.

Keywords: Cystic fibrosis; Steatorrhea; Pancreatic enzyme therapy; Compliance; Fecal chymotrypsin

A "vicious circle" of energy imbalance exists in cystic fibrosis (CF). Energy deficiencies result from imbalance between energy needs, energy supply and its effective use [1]. Loss of energy via the stool may be one of the factors leading to a gradual decline in body weight, ultimately influencing lung function and survival [2], therefore, exogenous pancreatic enzymes are an important part of CF therapy. The principles of pancreatic enzyme therapy (PET) have been described and discussed [1,3]. Optimization of pancreatic enzyme supplementation should result in medical (more efficient fat absorption, decrease of therapy-related risks), psychological (fewer capsules to be swallowed) and economic benefits (lower therapy costs).

Many CF patients are never tested for maldigestion [4], and efficacy of PET is not objectively assessed either. Baker et al. [5] failed to find any correlation between PET dose and gastrointestinal symptoms, and suggested that more sensitive outcome measures of the effectiveness of PET in cystic fibrosis (CF) patients are needed. The lack of objective assessment of PET efficacy in clinical settings remains a significant problem [2]. Most CF patients are instructed to take increasing PET doses without checking efficacy.

In addition to failure to test most CF patients for pancreatic function or PET efficacy, their compliance to PET, even in unresponsive and/or malnourished patients may not be subjected to objective measures either. Therefore, its real clinical importance remains unclear. The aim of the present study was to assess objectively patient's compliance to PET in CF subjects with unresponsive steatorrhea, using a combination of fecal elastase-1 and fecal chymotrypsin measurements.

1. Material and methods

The study was started in January 1999 and ended in December 2002. Subjects were selected out of a cohort of CF patients attending Department of Gastroenterology and Metabolism, Institute of Pediatrics, Poznan University of Medical Sciences and the Department of Pediatrics, Gastroenterology and Oncology, Institute of Pediatrics,

* Corresponding author. Tel.: +48 61 84800310; fax: +48 61 8483362.
E-mail address: jarwalk@am.poznan.pl (J. Walkowiak).

1569-1993/$ - see front matter © 2006 European Cystic Fibrosis Society. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.jcf.2006.05.006

Table 1
Basic clinical data of the studied CF patients (selection group, $n=8$)

Parameter	Mean±S.E.M. (range)
Age (years)	12.4±1.6 (5–19)
Fecal elastase-1 (μg/g)[a]	3.4±1.6 (0–11)
Steatorrhea (g/day)[a]	24.8±3.2 (16.4–43.1)
CFA (%)[a]	68.4±2.4 (59.8–78.4)
Energy intake (% RNI)	95.2±4.9 (72.5–116.1)
Fat intake (g/day)	79.3±8.1 (54.1–123.8)

[a] Normal values: Fecal elastase-1 > 200 μg/g of feces. Fecal fat excretion: 5–10 years < 5 g/day; more than 10 years < 7 g/day. CFA > 93.0.

Medical University in Gdansk, Poland. The protocol of the investigation was approved by the Ethical Committee of the Poznan University of Medical Sciences, Poland. All patients and their parents were asked to give an informed consent to participate the study.

1.1. Patients' selection

Inclusion criteria:

- Patients older than 5 years.
- Pancreatic insufficiency confirmed with fecal elastase-1 test and fecal fat balance study.
- Persistent steatorrhea (>15 g/day) when on high dose of PET (10 000 FIP lipase/kg of body weight/day).
- Willingness to participate the study.

Exclusion criteria:

- Coexistence of any gastrointestinal disease possibly influencing the assessment of pancreatic status and/or PET efficacy.

1.2. Subjects

One-hundred and five pancreatic insufficient CF patients with low fecal elastase-1 (E1) concentrations and abnormal fecal fat balance (without PET) were pre-selected for the study. In all pre-selected subjects, fecal fat excretion on PET was determined. Eight subjects (receiving maximal dose of PET i.e. 10 000 U lipase/kg of body weigh/day) fulfilled inclusion and exclusion criteria and were included in the study. Their basic clinical data are presented in Table 1.

In the 8 selected CF patients nutrient intake for 7 days was assessed. Fecal fat excretion was determined during the last 3 days of the nutritional assessment, and the coefficient of fat absorption (CFA) was calculated [6]. For the assessment of patients' compliance to PET, fecal chymotrypsin was measured in three independent samples during stool collection. In all CF patients with documented non-compliance, fecal chymotrypsin activity, fecal fat excretion and fat intake were subsequently assessed once PET recommendations had been followed.

1.3. Methods

Fecal elastase-1 concentration (the test based on monoclonal antibodies) was measured by an immunoenzymatic method (ELISA) [7], and fecal chymotrypsin activity was measured using a colorimetric method [8]. Fecal fat was analyzed according to van de Kamer et al. [9]. Daily fecal fat excretion was defined as a mean of a 72-h collection period.

The assessment of nutrient intake was based on the records of 7-day weighed rations. The records of 7-day weighed rations (with a use of scales accurate to 0.1 g) were collected at home. Parents and children were given both oral and written instructions for collecting diet records. The diet records were reviewed and clarified. The obtained data were analyzed using a computer database (Microsoft Access 7.0) prepared based on tables for the composition and nutrition value of food products [10]. The degree to which the recommended intake has been met was considered in relation to values given by the National Institute of Food and Nutrition in Warsaw [11]. For the examined group, moderate physical activity was assumed.

1.4. Statistical analysis

If not stated otherwise, values are expressed as mean± S.E.M.

2. Results

In 3 out of 8 CF patients with persistent steatorrhea, fecal chymotrypsin activities were lower than 6 U/g. Severe steatorrhea and low values of CFA were in concordance with low fecal chymotrypsin activities (Table 2). In the remaining five CF patients normal fecal chymotrypsin activities were found, which ranged from 11.3 to 55.2 U/g for single measurements and from 18.5 to 46.3 U/g for the mean value taken from three measurements of independent stool samples.

One of the patients that was documented to be non-compliant (No. 2) denied taking enzymes. Since the next fecal fat balance studies revealed less pronounced steatorrhea (25.5 and 18.3 g/day) and his nutritional status was normal (body height and weight above 50th centile) we accepted his position at that time. However, with progression of the pulmonary disease he started taking enzymes and he is

Table 2
Fecal tests in non-compliant CF patients

No.	Age (years)	Sex	Steatorrhea (g/day)	CFA (%)	Fecal chymotrypsin (U/g)		
1	5	F	18.9	65.1	UD	2.3	3.2
2	19	M	43.1	65.2	UD	UD	UD
3	12	M	32.5	59.8	6.8	1.1	UD

UD – undetectable.

Table 3
Changes in fat absorption and body weight in CF patients due to PET compliance

No	Without PET compliance			With PET compliance		
	Steatorrhea (g/day)	CFA (%)	Body weight *Z*-score	Steatorrhea (g/day)	CFA (%)	Body weight *Z*-score
1	18.9	65.1	−1.94	5.4	91.3[a]	−1.33
2	43.1	65.2	0.05	8.8	92.1[b]	−0.10
3	32.5	59.8	−1.75	8.9	90.2[a]	−1.35

[a] 6 months later.
[b] 2 years later.

continuing PET with a significant beneficial effect at present (Table 2).

The remaining two (Nos. 1 and 3) were instructed again how to follow PET recommendations. The compliance to PET resulted in significant decrease of fecal fat losses and the increase of CFA. A significant weight gain within the 3-month period was observed (Table 3).

3. Discussion

We have documented in the present study that non-treatable steatorrhea in some CF patients results from the lack of enzyme supplementation. Introduction of proper PET in three non-compliant subjects led to the significant decrease of fecal fat excretion. The increase of energy intake combined with the improvement of fat absorption resulted in significant weight gain. The introduction of PPIs was considered in the remaining 5 subjects once PET compliance had been documented.

Most CF patients are never tested either for pancreatic function or for PET efficacy or compliance. Borowitz et al. [4] proved that some CF patients were misclassified as pancreatic insufficient and underwent unwarranted therapy. The authors documented that some patients were also misclassified as pancreatic sufficient and were not recommended PET. Baker et al. [5] finding no correlation between PET dose and gastrointestinal symptoms suggested that more sensitive outcome measures of the effectiveness of PET in CF patients are needed. In addition, we have proved in the present study that subjective measures (history) might be not sufficient for checking PET compliance.

Determination of fecal chymotrypsin has been an accepted indirect test in pediatric practice for several years [8,12]. However, it has been shown that fecal elastase-1 is far more sensitive than fecal chymotrypsin in the assessment of exocrine pancreatic function in CF [13], and we have recommended that the fecal chymotrypsin test should be replaced by the fecal elastase-1 test in the initial determination of pancreatic status in CF. The fecal elastase-1 test (ELISA) is specific for the human enzyme and not influenced by exogenous enzyme supplementation [14], whereas due to the colorimetric method used, the measurement of chymotrypsin activity is affected2 by enzyme substitution therapy [15]. Thus, for the assessment of endogenous pancreatic secretion using fecal chymotrypsin, PET should be stopped for at least 3 days before the test. On the other hand, the interference by exogenous enzymes creates the possibility to check adherence to recommended pancreatic enzyme supplementation by the measurement of chymotrypsin activity.

In conclusion, all unresponsive and/or malnourished CF patients should undergo routine check-up with fecal assay for PET compliance.

Acknowledgements

This investigation was supported in part by the Polish Scientific Research Committee.

References

[1] Sinaasappel M, Stern M, Littlewood J, Wolfe S, Steinkamp G, Heijerman HG, et al. Nutrition in patients with cystic fibrosis: a European Consensus. J Cyst Fibros 2002;1:51–75.
[2] Walkowiak J. Assessment of maldigestion in cystic fibrosis. J Pediatr 2004;145:285–7.
[3] Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 2002;35:246–59.
[4] Borowitz D, Baker SS, Duffy L, Baker RD, Fitzpatrick L, Gyamfi J, et al. Use of fecal elastase-1 to classify pancreatic status in patients with cystic fibrosis. J Pediatr 2004;144:322–6.
[5] Baker SS, Borowitz D, Duffy L, Fiztpatrick L, Gyamfi J, Baker RD. Pancreatic enzyme therapy and clinical outcomes in patients with cystic fibrosis. J Pediatr 2005;146:189–93.
[6] Walkowiak J, Nousia-Arvanitakis S, Henker J, Stern M, Sinaasappel M, Dodge JA. The use of indirect pancreatic function tests in children. J Pediatr Gastroenterol Nutr 2005;40:107–14.
[7] Scheefers-Borchel U, Scheffers H, Arnold R, Fischer P, Sziegoliet A, Scheefers-Borchel U, et al. Pankreatische elastase-1: parameter für die chronische und akute pankreatitis. Lab Med 1992;16:427–34.
[8] Brown GA, Sule D, Williams J, Puntis JW, Booth IW, McNeish AS. Faecal chymotrypsin: a reliable index of exocrine pancreatic function. Arch Dis Child 1988;63:185–9.
[9] Van de Kamer JH, Bokkel-Huinik HB, Weyers HA. Rapid method for determination of fat in feces. J Biol Chem 1949;177:347–55.
[10] Kunachowicz H, Nadolna I, Przygoda B. Nutritional value of ford products. Warszawa: Instytut Żywności i Zywienia; 2005. p. 1–671. [in Polish].
[11] Ziemlański S, Bulka-Jachymczyk B, Budzynska-Topolowska J. Recommended nutrient intake for Polish population (energy, protein, fat, vitamins, macro- and micronutrients). Żyw Człow Metab 1994;21:303–38 [in Polish].
[12] Girella E, Faggionato P, Benetazzo D, Mastella G. The assay of chymotrypsin in stool as a simple and effective test of exocrine pancreatic activity in cystic fibrosis. Pancreas 1988;3:254–62.
[13] Walkowiak J, Herzig KH, Strzykala K, Przyslawski J, Krawczynski M. Fecal elastase-1 is superior to fecal chymotrypsin in the assessment of pancreatic involvement in cystic fibrosis. Pediatrics 2002;110:E1–7.
[14] Walkowiak J. Fecal elastase-1 test – clinical value in the assessment of exocrine pancreatic function in children. Eur J Pediatr 2000;159:869–70.
[15] Stein J, Jung M, Sziegoleit A, Zeuzem S, Caspary WF, Lembcke B. Immunoreactive elastase 1: clinical evaluation of a new noninvasive test of pancreatic function. Clin Chem 1996;42:222–6.