

Antibiotic therapy and fat digestion and absorption in cystic fibrosis

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Antibiotic therapy in the cystic fibrosis (CF) mouse model has been shown to result in reduced bacterial load of the intestine and significant body mass gain. The effect was suggested to be linked to the improvement of intestinal digestion and absorption. Therefore, we aimed to assess the influence of routinely applied antibiotic therapy in CF patients on fat assimilation. Twenty-four CF patients aged 6 to 30 years entered the study. Inclusion criteria comprised confirmed exocrine pancreatic insufficiency and bronchopulmonary exacerbation demanding antibiotic therapy. Exclusion criteria comprised: antibiotic therapy six weeks prior to the test, liver cirrhosis, diabetes mellitus, oxygen dependency, the use of systemic corticosteroids. In all enrolled CF subjects, ¹³C-labelled mixed triglyceride breath test (¹³C MTG-BT) was performed to assess lipid digestion and absorption, before and after antibiotic therapy. Sixteen subjects were treated intravenously with ceftazidime and amikacin, eight patients orally with ciprofloxacin. Cumulative percentage dose recovery (CPDR) was considered to reflect digestion and absorption of lipids. The values are expressed as means (medians). The values of CPDR before and after antibiotic therapy did not differ in the whole studied group [4.6(3.3)% vs. 5.7(5.3)%, $p=0.100$] as well as in the subgroup receiving them intravenously [4.6(3.2)% vs. 5.7(5.3)%, $p=0.327$] or in that with oral drug administration [4.6(3.4)% vs. 5.7(5.4)%, $p=0.167$]. In conclusion, antibiotic therapy applied routinely in the course of pulmonary exacerbation in CF patients does not seem to result in an improvement of fat digestion and absorption.

Keywords: cystic fibrosis, antibiotic therapy, malabsorption, stable isotope breath test

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INTRODUCTION

Cystic fibrosis (CF) is an inflammatory and destructive disease with differentiated clinical expression. Bronchopulmonary disease is the major clinical manifestation which frequently demands antibiotic therapy. Available data suggests that such treatment applied in CF patients improves not only respiratory function but also nutritional status, which has been related to increased energy intake and decreased energy expenditure (Vic *et al.*, 1997; Castro *et al.*, 2002; Hankard *et al.*, 2002; Béghin *et al.*,

2003). Interestingly, antibiotic therapy in the CF mouse model resulted in the reduction of bacterial load of the small intestine, decreased intensity of intestinal inflammation and significant body mass gain. The effect was suggested to be linked to the improvement of intestinal digestion and absorption (Norkina *et al.*, 2004a; 2004b). Therefore, we aimed in the present study to assess the influence of routinely applied antibiotic therapy in CF patients on fat digestion and absorption.

MATERIAL AND METHODS

The study comprised 24 CF patients (14 females and 10 males) (Table 1). Diagnosis of CF was based on history, clinical manifestation and increased sweat chloride concentrations and confirmed by the *CFTR* gene analysis. The genotypes of the studied patients were as follows: F508del/F508del ($n=11$), F508del/*CFTR*dele2,3 (21 kb) ($n=2$), F508del/R553X ($n=1$), F508del/2143delT ($n=1$), *CFTR*dele2,3 (21 kb)/*CFTR*dele2,3 (21 kb) ($n=1$), 1717-1G-A/N1303K ($n=1$), F508del/2143delT ($n=1$), F508del/2183AA-G ($n=1$), F508del/W1282X ($n=1$), 1717-1G-A/N1303K ($n=1$), F508del/unknown mutation ($n=2$), unknown mutation/unknown mutation ($n=1$).

Inclusion criteria for subjects comprised the willingness to participate in the study and exocrine pancreatic insufficiency (fecal elastase-1 concentration <100 $\mu\text{g/g}$ and the presence of steatorrhea) (Walkowiak, 2004; Walkowiak *et al.*, 2005). Exclusion criteria comprised: intravenous and oral antibiotic therapy six weeks prior to the test, liver cirrhosis, diabetes mellitus, oxygen dependency, the use of systemic corticosteroids.

In all enrolled CF subjects, ¹³C-labelled mixed triglyceride breath test (¹³C MTG-BT) was performed to assess lipid digestion and absorption, before and after antibiotic therapy (on the day preceding antibiotic therapy and on the last day of antibiotic administration). Sixteen patients were treated intravenously with ceftazidime and amikacin, in respective doses: 150–250 mg/kg per 24 h and 20–35 mg/kg per 24 h, the remaining eight subjects were given ciprofloxacin orally in a dose of 35–50 mg/

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Abbreviations: CF, cystic fibrosis; *CFTR*, cystic fibrosis transmembrane conductance regulating protein; ¹³C MTG-BT, ¹³C-labelled mixed triglyceride breath test; CPDR, cumulative percentage dose recovery; CFA, coefficient of fat absorption

Table 1. Basic epidemiological and clinical data of cystic fibrosis patients (n=24)

Parameter	Range	Mean (median)
Age (years)	10–32	19.8 (18)
Body mass (Z-score)	-2.42–1.02	-0.89 (-0.94)
FEV1 ^a (%)	55–105	78 (77)
Fecal elastase-1 (µg/g)	BDL ^b –88	12 (7)
AIAT ^c (U/l)	8–52	24.4 (24)
GGTP ^d (U/l)	6–98	18.9 (14)

^aforced expiratory volume in 1 s; ^bbelow detection limit; ^calanine transaminase (EC 2.6.1.2); ^dγ-glutamyltransferase (EC 2.3.2.2)

kg per 24 h. The antibiotics were administered for 14 days.

¹³C MTG-BT was performed after overnight fast. Each of the studied subjects received 150 mg of ¹³C mixed triglyceride with 0.25 g butter per kg body mass mixed on a slice of bread. Breath samples were collected at baseline (fasting) and at 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330 and 360 minutes after test meal ingestion. The samples were analyzed with an IRIS ¹³C-Analyser System (Wagner, Bremen, Germany). Cumulative percentage dose recovery (CPDR) was considered to reflect digestion and absorption of lipids.

Values are expressed as ranges, means and medians. The statistical significance of differences in CPDR before and after antibiotic therapy was determined with the use of Wilcoxon-rank test. The level of significance was set at $p < 0.05$. Statistical analysis was performed using STATISTICA 8.0. (StatSoft Inc. 2008).

The protocol of the investigation was approved by the Bioethical Committee of Poznań University of Medical Sciences, Poland.

RESULTS

The values of CPDR before and after antibiotic therapy did not differ in the whole studied group or in either of the subgroups differing in the mode of drug administration (Table 2).

DISCUSSION

No significant influence of the antibiotic treatment applied on lipid digestion and absorption was observed in

the present study. To the best of our knowledge this is the first study assessing such a relationship in humans in a reliable way.

Reilly *et al.* (1999) made an attempt to assess the effect of an acute respiratory exacerbation on energy balance. The exacerbation was associated with a significant reduction in energy intake. A trend towards lower total energy expenditure was observed. No statistical differences in fat absorption and resting energy expenditure as well as body mass and composition were documented. However, the power of the study was rather low, as only 14 children were studied. The data on the effectiveness of fat digestion and absorption (coefficient of fat absorption — CFA) were available for ten of them. CFA was better during exacerbation in seven subjects and worse in one patient. The authors attributed some CFA changes to a better compliance with the pancreatic enzyme replacement therapy under supervision. However, they finally concluded that the changes were negligible. With the methodology applied in their study it is difficult to determine the reliability of the findings. Fat intake was assessed during exacerbation for 6–7 days and for one weekend and two week days during the stable period. Fecal fat output was calculated from a three-day stool collection made during each period. Nevertheless, the relationship between the timing of food intake and stool collection as well as between stable period, antibiotic treatment and exacerbation was not precised. According to the authors' discussion they aimed to assess the difference in CFA between well-being and exacerbation. In contrast to their study, we assessed the effect of both oral and intravenous antibiotic therapies. In addition, we determined fat assimilation on fixed days before and after antibiotic treatment (reflecting in a reliable way appropriate time points) to assess its potential influence on the efficacy of digestion and absorption.

There is a strong association of bacterial infection and inflammation in CF, at least in the airways. Accumulating evidence indicates that susceptibility to inflammation may be inherent to the tissue involved even in the absence of specific pathogenic microbial colonization (Muhlebach *et al.*, 1999). The CFTR-null mouse model does not express CFTR and is not expected to have inherent inflammation due to protein misfolding. The observed inflammation in the CF mouse intestine most likely occurs as a result of altered luminal environment with subsequent bacterial overgrowth (Norkina *et al.*, 2004a; 2004b). The body weight of CF mice at the end of 3-week antibiotic treatment (ciprofloxacin and metronidazole) was significantly increased compared to untreated CF mice and not significantly different from that of wild-type animals. The antibiotic treatment had no effect on the body mass of control wild-type animals (Norkina *et al.*, 2004b). The obtained results suggest that antibiotic therapy may have a significant impact on digestion and absorption in CF patients, thereby influencing the energy balance during treatment of pulmonary exacerbations. The doses used in the animal model are not easy to be translated into a human study. Moreover, ciprofloxacin doses used in bronchopulmonary exacerbation in CF are well established. Therefore, we applied its typical

Table 2. Lipid digestion and absorption in cystic fibrosis (CF) patients undergoing antibiotic therapy based upon cumulative ¹³C dose recovery (CPDR)

Studied group (n)	CPDR			Statistical significance
	Parameter	Before	After	
CF (24)	Mean (median)	4.6 (3.4)	5.8 (5.3)	$p = 0.100$
	Range	0–20.2	0.8–12.8	
CF-IV* (16)	Mean (median)	4.6 (3.2)	5.7 (5.3)	$p = 0.327$
	Range	0–20.2	1.8–11.4	
CF-PO** (8)	Mean (median)	4.7 (3.4)	5.7 (5.4)	$p = 0.167$
	Range	0–9.5	0–12.8	

*CF-IV, subjects receiving antibiotics intravenously; **CF-PO, subjects receiving antibiotics orally

doses. Although intravenous therapy in such cases is more commonly used, we also assessed the effects of oral antibiotic administration on lipid assimilation. The observed changes did not reach the level of significance. However, a tendency towards an improvement of fat absorption was noted.

In conclusion, routinely applied antibiotic therapy in the course of pulmonary exacerbation in CF patients does not seem to result in an improvement of fat digestion and absorption.

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