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ORIGINAL CONTRIBUTION

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Faecal elastase-1 and fat-soluble vitamin profiles in patients with cystic fibrosis in Western Norway

Summary *Background* Exocrine pancreatic insufficiency is a major clinical manifestation of cystic fibrosis (CF). Almost nine of ten patients develop signs and symptoms of maldigestion and malabsorption, which often deteriorates nutritional status and therefore worsens the prognosis. Human faecal elastase-1 (FE-1) has shown promising results to assess exocrine pancreatic insufficiency, and this test has been used at Haukeland University Hospital since 1996. *Aim of the study* To evaluate FE-1 values and fat-soluble vitamin profiles in patients with CF and to correlate exocrine pancreatic function as measured as FE-1 to fat-soluble vitamin profiles. Moreover, we wanted to assess if there are differences between fat-soluble vitamin profiles in patients with impaired versus patent exocrine pancreatic function, and thirdly, if fat-soluble vitamin deficiency at diagnosis is effectively treated by supplementation. *Methods* Consecutive analyses (N = 212) of fat-soluble vitamin profiles and 35 analyses of FE-1 were investigated in 35 patients with CF. In 17 out of 35 patients fat-soluble vitamin profiles were also assessed at diagnosis. *Results* Mean value of FE-1 for all CF patients was 256.9 µg/g faeces (median 24.1 µg/g faeces). CF patients considered to have maldigestion (N=24) showed a mean value of 19.9 µg/g faeces (median 18.7 µg/g faeces), those without pancreas affection had a mean value of 773.9 µg/g faeces (median 728.9 µg/g faeces, $p < 0.01$). There was no difference in fat-soluble vitamin profiles among patients with or without exocrine pancreatic insufficiency while on appropriate supplementation. Median value for vitamin E in patients with exocrine pancreatic insufficiency at diagnosis was low (3.6 mg/L). Supplementation of pancreatic enzymes and vitamins normalised profiles in this group at follow-up. There was no significant correlation between exocrine pancreatic function as measured as FE-1 and fat-soluble vitamin profiles, neither in patients with impaired nor in those with patent pancreatic function. *Conclusions* Severe degree of exocrine pancreatic insufficiency is common in patients with cystic fibrosis. There was no correlation of faecal elastase-1 levels to fat-soluble vitamin status. Fat-soluble vitamins (A, D, E) given in appropriate dosages combined with pancreatic enzymes ensured normal profiles in our patients with CF and malabsorption. Officially recommended supplementation of vitamin A and D in Norway during infancy and childhood may explain why so few patients had vitamin deficiencies at diagnosis.

Key words cystic fibrosis – faecal elastase-1 – exocrine pancreatic insufficiency – maldigestion – fat-soluble vitamins

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Introduction

Maldigestion due to exocrine pancreatic insufficiency is a major clinical manifestation of cystic fibrosis (CF). It leads to massive fat and protein losses and affects the nutritional status of patients with CF. Its recognition is important for proper diagnosis and management. By late childhood, 85–90 % of all patients have steatorrhea. The exocrine pancreas has an enormous func-

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tional reserve. More than 98 % of its exocrine capacity must be lost before signs of maldigestion become evident [1].

Faecal elastase-1 (FE-1) has been evaluated to be a reliable tool to measure exocrine pancreatic function [2–4]. Its measurement is not influenced by pancreatic enzyme substitution. Several other tests to evaluate exocrine pancreas function, either direct or indirect, have drawbacks and none of these tests is ideal [3, 5].

Nutritional status and its support are widely recognised as an integral part of the multidisciplinary patient care in the CF setting and are considered to be an important predictor of outcome. Long-term follow-up of CF patients has shown significantly better survival in patients who had achieved normal nutritional status [6]. Up to 15 % of oral energy intake is lost in the stools despite pancreatic enzyme replacement [7]. In addition to impaired pancreatic enzymes, this is due to variable decreased bicarbonate, bile salt disturbances and hepatobiliary dysfunction. Fat-soluble vitamin deficiencies are common in CF. Their profiles are helpful in the assessment of nutritional status and are therefore performed annually in most CF centres like in ours.

The aim of the study was to evaluate FE-1 values and fat-soluble vitamin profiles in our patients with CF and to correlate exocrine pancreatic function as measured as FE-1 to fat-soluble vitamin profiles. Moreover, we wanted to assess if there were differences between fat-soluble vitamin profiles in patients with impaired versus patent exocrine pancreatic function, and thirdly, if fat-soluble vitamin deficiency at diagnosis is effectively treated by supplementation.

Patients and methods

Haukeland University Hospital serves as a regional centre for CF patients in Western Norway. The study included 35 patients from our cohort of patients with CF with a median age of 10 years. General patient data are shown in Table 1.

The CF diagnosis was made by demonstration of repeated elevated sweat chloride concentrations and typical clinical manifestations in all patients. Twelve patients were found to be homozygous for the dF508 mutation (34 %); the remaining 23 patients had either two other mutations (4 patients), one detectable mutation (8 patients) or no mutation has been found so far (11 patients).

Our patients attended the outpatient department every 2nd–3rd month, or more often when needed. Seven patients (20 %) had chronic lung infection with *Pseudomonas aeruginosa*, and they have been given 12-day courses of intravenous antibiotic treatment every third month.

Fat-soluble vitamins (A (retinol), 25-OH-vitamin D and E (alpha-tocopherol)) were measured [8] yearly at follow-up, and we performed 212 consecutive analyses between 1992 and 2001. In 17 out of 35 patients fat-soluble vitamin profiles were also assessed at diagnosis. FE-1 was measured as part of assessment of the exocrine pancreatic function. FE-1 was determined with a commercial sandwich ELISA kit (ScheBo Tech GmbH, Wettenberg, Germany), which uses two monoclonal antibodies against different specific epitopes of human pancreatic elastase. Measurement of the optical density was performed with Multiscan EX (Labsystems, Espoo, Finland).

Concentrations of elastase-1 above 200 µg/g faeces were considered as normal, values between 100–200 µg/g faeces were reflecting moderate exocrine pancreatic insufficiency, and values below 100 µg/g faeces were taken as a sign of severe deficiency.

Daily vitamin supplementation consisted of a standard multivitamin preparation (e. g. Biovit®, Nycomed) 20 ml (double dose) containing per millilitre 50 µg vitamin A, 0.75 µg vitamin D_3 and 0.6 mg vitamin E plus water-soluble vitamins or ordinary dose plus cod liver oil. Vitamin E (Ido-E®, Pharmacia & Upjohn) was provided at a dose of 50–200 mg daily. Supplementation of pancreatic enzymes consisted of 5000–10 000 IE lipase per kilogram bodyweight per day.

Data analysis was performed using a commercially available software package (SPSS). Descriptive statistics included mean, minimum and maximum values, standard deviations and median. Differences in FE-1 between patients with patent or impaired exocrine pancreatic function were tested by Student's *t* test. The relation between fat-soluble vitamins and FE-1 were assessed by the Pearson correlation coefficient. Reported p values are two-tailed and $p < 0.05$ was considered statistically significant.

Table 1 General patient data for 35 patients with cystic fibrosis, mean values ± standard deviation; range is shown in parentheses

	N=35
Age (years)	12.1 ± 8.9 (2–40)
Sex ratio (f/m)	16/19
Chloride sweat in mmol/L	102.7 ± 23.5 (62–157)
Pancreatic enzyme supplementation	25

Results

The mean FE-1 value of our 35 patients with CF was 256.9 ± 445.2 µg/g faeces (median value: 24.1 µg/g faeces). Patients with maldigestion (N= 24) had a mean value of 19.9 ± 15.8 µg/g faeces (median value: 18.7 µg/g faeces). Patients without pancreas affection (N= 11) had a mean value of 773.9 ± 494.4 µg/g faeces (median:

Table 2 Laboratory findings of 17 patients with cystic fibrosis at diagnosis and follow-up (on supplementation); values are mean ± SD; range is shown in parentheses (*PI* pancreas insufficient, *PS* pancreas sufficient)

	PI (N= 9)		PS (N= 8)	
	at diagnosis	on supplementation	at diagnosis	on supplementation
FE-1 (µg/g faeces)	14.4 ± 16.5* (0–42)		631 ± 368 (261–1147)	
Serum vitamin A (retinol, µg/L) Normal: > 200 µg/L	367 ± 137 (155–558)	347 ± 81.3 (228–475)	340 ± 107 (185–505)	379 ± 85.2 (228–505)
25-OH-vitamin D (nmol/L) Normal: 25–130 nmol/L	50.3 ± 24.8 (15.1–92.8)	60.5 ± 26.2 (17.5–92.8)	55.3 ± 19.4 (17.9–77.9)	71.0 ± 29.5 (34.5–132.8)
Serum vitamin E (alpha-tocopherol, mg/L) Normal: > 5 mg/L	7.0 ± 6.6 (1.4–19.3)	9.8 ± 2.7 (5.9–12.9)	6.9 ± 2.6 (3.9–7.7)	9.1 ± 3.3 (5.2–14.9)

* $p < 0.01$ between PI and PS

728.9 µg/g faeces, $p < 0.01$). All 24 patients with exocrine pancreatic insufficiency had FE-1 values lower than 60 µg/g faeces.

Fat-soluble vitamin profiles at diagnosis and at follow-up for 17 CF patients are presented in Table 2.

All mean values are in normal range, except vitamin E in patients with exocrine pancreatic insufficiency. Five out of nine patients (55%) in this group had hypovitaminosis E at diagnosis with a mean value of 7.0 ± 6.6 mg/L (median 3.6 mg/L). The levels were corrected at follow-up in these five patients (mean value of 9.8 ± 2.7 mg/L, median 10.8 mg/L). One of these five patients with exocrine pancreatic insufficiency had an additional vitamin A and D deficiency at diagnosis. The vitamin A level was corrected, whereas the D level still remained low at follow-up.

Two patients with patent pancreatic function had hypovitaminosis. One of them had a combined vitamin A and E deficiency at diagnosis, which was corrected at follow-up. The other one had vitamin D deficiency at diagnosis, normalised at follow-up.

Mean values of fat-soluble vitamins at follow-up for 35 patients with CF did not differ significantly between patients with sufficient and insufficient pancreatic function, and they were all in normal range (Table 3).

Three patients with exocrine pancreatic insufficiency had hypovitaminosis at follow-up. Two patients had hypovitaminosis E (mean 3.4 mg/L and mean 4.7 mg/L), one patient had hypovitaminosis D (mean 17.5 nmol/L); none had hypovitaminosis A.

There were no correlations between exocrine pancreatic function as measured as FE-1 and different fat-soluble vitamin profiles neither at diagnosis, nor during treatment at follow-up in our CF patients ($r=0.282$, $p < 0.100$). Fig. 1 shows a plot of vitamin E profiles and the corresponding FE-1 values.

Table 3 Laboratory findings of 35 patients with cystic fibrosis on supplementation; values are mean ± SD; range is shown in parentheses (*PI* pancreas insufficient, *PS* pancreas sufficient)

	PI (N= 24)	PS (N= 11)
FE-1 (µg/g faeces)	19.9 ± 15.8* (0–57.3)	774 ± 494 (261–1927)
Serum vitamin A (retinol, µg/L) Normal: > 200 µg/L	386 ± 97.0 (228–563)	385 ± 76.0 (228–505)
25-OH-vitamin D (nmol/L) Normal: 25–130 nmol/L	54.1 ± 21.0 (17.5–98.9)	63.9 ± 27.8 (33.6–133)
Serum vitamin E (alpha-tocopherol, mg/L) Normal: > 5 mg/L	9.1 ± 2.7 (3.4–12.9)	9.8 ± 4.2 (5.2–18.9)

* $p < 0.01$ between PI and PS

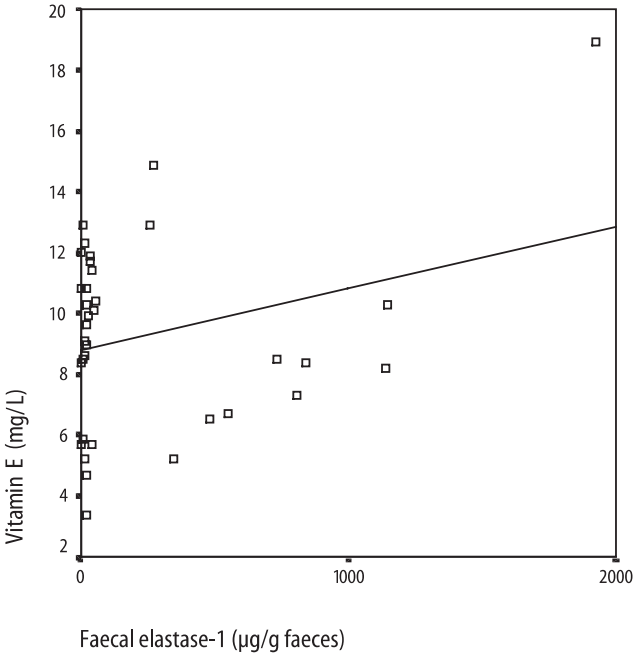

Fig. 1 Vitamin E profiles and FE-1 values in 35 patients with cystic fibrosis at follow-up ($r=0.282$, $p < 0.100$).

Discussion

All our CF patients with exocrine pancreatic insufficiency had low levels of faecal elastase-1, indicating a severe degree of malfunction, and all have been treated with pancreatic enzymes. Only one patient with low normal FE-1 value (260.7 μg/g faeces) has been dependent on pancreatic enzyme supplementation.

The sensitivity and specificity of FE-1 has been evaluated to be 96 % and 100 %, respectively [9], which makes this test the most attractive "tubeless" pancreatic function test, especially in paediatric patients. Twenty of 22 CF patients had extremely low values (< 20 μg/g faeces) in the study performed by Gullo and coworkers, whereas 27 healthy children had values of greater than 500 μg/g.

There was, unexpectedly, no correlation between exocrine pancreatic function as measured as FE-1 and fat-soluble vitamin profiles in our patients. This has not been described before, although the dependency of fat-soluble vitamin profiles on maldigestion is well known [10]. This lack of a correlation could have several explanations. Official nutritional guidelines in Norway advise vitamin A and D supplementation from four weeks of age and throughout childhood, because of the northern climate and reduced exposure to sunlight during the winter months. Intake of cod liver oil has been encouraged, the recommended five millilitres of cod liver oil contain 500 μg vitamin A, 10 μg vitamin D_3 and 10 mg vitamin E. Patients with CF thus might have a better fat-soluble vitamin status at diagnosis than one would have expected if vitamin supplementation had not been given. This is further substantiated by the observation that patients on treatment had low mean levels only if extra supplementation with fat-soluble vitamins were not taken consequently.

CF patients in Norway seem to run a more favourable course than in many other countries. The prevalence of chronic Pseudomonas aeruginosa lung infection in Norway is 35 %, and in the patient cohort from western Norway presented here the prevalence is 20 %, which is very low.

Mutations in Norwegian CF patients are not fully revealed yet. One mutation described at the Department of Medical Genetics in our hospital (4005+2T > C, Helge Boman, personal communication) has not been found in CF patients outside Norway. This mutation seems to protect against pancreatic insufficiency, even when occurring together with the delta F508 mutation. There might well be other mutations carrying a better prognosis than usually among CF patients elsewhere.

Profiles of fat-soluble vitamins are considered to be helpful in the assessment of nutritional status in CF. Appropriate supplementation of fat-soluble vitamins and pancreatic lipase are important in the management of CF. Deficiency of fat-soluble vitamins has been demonstrated at diagnosis in CF patients [11] like in our patients with pancreatic insufficiency at diagnosis (vitamin E).

Annually follow-up of these parameters is part of clinical routine procedures at most CF centres. Despite supplementation, deficiency of fat-soluble vitamins may be seen even when treated with pancreatic enzymes [10], a finding, which we could not confirm in our patients. A consensus report on nutrition in CF identified vitamin A and E to be of particular concern [12, 13]. Vitamin E is an antioxidant and may have a role in the protection of lung tissue against oxidative damage [14].

Vitamin D and K have been recently considered to play an important role in the context of bone demineralisation in CF. Intervention in early childhood is probably beneficial [15–17]. Fragility fractures and hypovitaminosis D occur commonly in adult patients with CF [18] and an oral fat-soluble vitamin combination with a modest amount of vitamin K can improve the PIVKA-II levels in patients with pancreatic insufficiency [19]. We intend to look at bone density abnormalities in our CF cohort in the near future.

Our study showed values of fat-soluble vitamins mostly in the normal range both in patients with maldigestion and patent pancreas function at follow-up. This may be an indication of appropriate enzyme and vitamin supplementation both before and after diagnosis and may reflect good patient compliance. Profiles taken before treatment in patients newly diagnosed with exocrine pancreatic insufficiency showed low values for vitamin E in more than half of the patients. Once treated, they were normalised at follow-up. The results of our study should be seen in the light of officially recommended supplementation of vitamin A and D in Norwegian infants and children.

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