Original Communication

Self-reported use of vitamins and other nutritional supplements in adult patients with cystic fibrosis. Is daily practice in concordance with recommendations?

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Abstract: *Background:* In cystic fibrosis (CF), prophylactic supplementation of the fat-soluble vitamins A, D, E, and K is recommended. Limited data is available describing vitamin prescription adherence by adult patients. The aim of this study was to assess the use of prescribed vitamins and other nutritional supplements by adult CF patients.
Methods: All adult CF patients (n = 111) registered at the Utrecht CF Center were invited to participate in a telephone survey on supplement use. Supplemental vitamin intakes were compared with recommendations. In a subsample, associations between supplemental intake and serum vitamin D and E values were assessed.
Results: In this study 80 % of the patients reported the use of vitamin and/or mineral supplements. Fat-soluble vitamins were used by 43 % of pancreatic-sufficient (PS) and 81 % of pancreatic-insufficient (PI) patients. Of PI patients reporting supplemental vitamin use, only 9 % met the recommendations for vitamin A, 32 % for vitamin D, 59 % for vitamin E, and 81 % for vitamin K. Multivitamin supplements were used by 42 % of PI and by 29 % of PS patients. Other nutritional supplements were rarely used.
Conclusion: A high percentage of PI patients use fat-soluble vitamins below recommendations. Therefore adequate monitoring of vitamin supplementation and status is warranted.

Key words: Vitamins, cystic fibrosis, self-reported use, adult patients, recommendations, fat-soluble vitamins, pancreatic-insufficient.

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Introduction

Deficiencies of the fat-soluble vitamins A, D, E, and K are common in cystic fibrosis (CF) due to pancreatic insufficiency (PI), disturbances in bile salt metabolism, and hepatobiliary dysfunction. Many patients have deficiencies at the time of CF diagnosis [1]. In a study of infants diagnosed by newborn screening (age range 0–3 months), 60 % were deficient for vitamin A, 37 % for vitamin D, and 16 % for vitamin E [2].

Despite supplementation with standard multivitamins and pancreatic enzymes, sporadic occurrences and persistent deficiencies of fat-soluble vitamin deficiencies remain relatively common in CF patients [3–6]. The role of fat-soluble vitamins in CF has been reviewed [7] and it was concluded that optimal status of the fat-soluble vitamins is an important treatment goal which can affect health status in a positive manner. European CF guidelines recommend prescription of prophylactic supplementation of vitamin A (4000–10,000 IU/day); vitamin D (400–800 IU/day); vitamin E (100–400 IU/day); and vitamin K (1 mg/day to 10 mg/week) [8] for CF patients with pancreatic insufficiency (PI). The need for either fat- or water-soluble vitamin supplementation in patients who are pancreatic-sufficient (PS) should be assessed on an individual basis according to normal dietary intake and plasma levels. In our Dutch CF center, patients are advised to use fat-soluble vitamins A, D, and E. Vitamin K is supplemented based on plasma status. In clinical practice vitamin K supplementation is mainly prescribed for patients with severe malnutrition or liver insufficiency.

Other supplements may also be used in this patient population. For a number of nutrients, there are indications that uptake and status may be affected by CF. For example, calcium uptake in the intestine might be reduced due to low vitamin D levels and fat malabsorption [9]. Deficiencies of water-soluble vitamins are rare in CF, but may exist [10, 11].

Data on the use of vitamin and other nutritional supplements in CF patients is limited. A recent survey of all UK pediatric CF centers showed that vitamins A, D, and E are routinely prescribed by most centers, but only 18 % of centers routinely prescribe vitamin K [12]. It has been shown that adherence to prescribed vitamin treatment is lower in adolescent patients than in children with CF (57 % and 85 % respectively) [13]. In adults even lower compliance to prescribed vitamins (47 %) was observed in a study in the UK [14]. In a study amongst adults in the USA, 88 % of adult CF patients reported the use of a CF-specific multivitamin supplement [15]. In this study it was additionally shown that 25 % of adult CF patients reported the use of calcium supplements and 52 % reported use of standard multivitamin supplements [15].

The aim of this study was to assess the use of vitamins and other nutritional supplements by adult CF patients registered at the CF Center Utrecht, the Netherlands, and to compare the supplemental intake of vitamin A, D, E, and K with the recommended doses as described in the European Consensus guidelines. In addition, the associations between supplemental intake and serum levels of vitamin D and E were described in a subsample.

Subjects and methods

Study population

All 111 outpatient adult CF patients (110 Caucasian and 1 Hispanic) registered at the CF Center were invited to take part in a telephone survey on the use of supplements. First, a letter was sent to all patients to explain the purpose of the study and to ask permission to contact them by phone. If patients were unwilling to participate, they were asked to return a postage-free refusal form. The Medical Ethical Committee of the University Medical Center Utrecht provided permission to contact the patients. The study was conducted in June 2005.

Use of supplements

A dietitian performed the telephone survey. The patients were asked if they used dietary supplements such as vitamins (A, B, C, D, E, and K), minerals (calcium, iron, and others), fish oil capsules, and/or creatine. These supplements were selected based on earlier reports and because patients regularly ask questions concerning these supplements during clinic visits. Secondly, the patients were asked on whose advice (physician, dietitian, own initiative) the supplements were taken. Finally the brand name, the frequency of use (per day), the dose (capsule/tablet per day), and the duration of use (in months) of supplements were documented.

Composition of supplements

The composition of the supplements was determined by a dietitian using the Compendium on Food supplements 2005 [16]. If necessary, additional information

on the composition of specific supplements was sought on the Internet. If no information could be found, patients were requested to send in the package inserts of used supplements. Subsequently, based on the dose and frequency of use, the mean daily supplemental intake of vitamins A, B, C, D, E, and K, and calcium was calculated for each patient. For this purpose, intake from single-nutrient supplements and multivitamins were combined. Intake of the fat-soluble vitamins was compared with the recommendations for CF patients as described in the European Consensus [8].

Nutritional status and serum vitamin levels

Data on height and weight were collected from medical records. Body mass index was calculated [weight (kg)/height (m)2]. When available, we collected data from medical records on serum levels of vitamin D and vitamin E. As part of patients' annual comprehensive clinical evaluations, non-fasting blood samples were obtained for determination of 25-hydroxyvitamin D (41 PI patients) and vitamin E (39 PI patients). Serum 25-hydroxyvitamin D was measured with radioimmunoassay after extraction with acetonitrile (DiaSorin, Minnesota, USA). Serum vitamin E was assessed by high-pressure liquid chromatography (HPLC) with UV-detection. Serum values for vitamins A and K were not available.

Data entry and analysis

Means, standard deviations and ranges of vitamin and mineral intake were calculated. Differences between groups were tested with the Student's t-test (means) or Pearson chi-square test (proportions). Pearson correlation coefficients were calculated between supplemental intake and serum levels of vitamins D and E. All analyses were performed using SPSS. A p-value < 0.05 was considered statistically significant.

Results

Participation

Of the 111 patients who were invited to take part in the survey, 93 (84 %) patients agreed to participate. One patient had died, six patients refused participation, and eleven patients could not be contacted. The mean age in the non-responders was slightly higher than in the responders, but this difference was not significant (32 versus 28 years, $p = 0.17$). Responders and non-responders did not differ significantly by gender and pancreatic status.

Of the 93 patients, 74 (80 %) reported the use of vitamin and/or mineral supplements on a daily or weekly basis. One patient reported incidental supplement use (a few times per year) which was considered as "no use." Men were more often non-users than women (27 % versus 12 %), although this difference did not reach statistical significance ($p = 0.07$). In Table I, general characteristics and supplement use are reported separately for PI and PS patients. A higher mean body mass index was observed for the PS patients than the PI patients (23.6 versus 21.0 kg/m^2; $p = 0.001$).

Use of the fat-soluble vitamins A, D, E, and K

When compared to PI patients, the overall use of fat-soluble vitamins was lower in PS patients [Table I]. Vitamin E was the most frequently used single-nutrient supplement in PI patients (63 %). In the PI group, 29 (37 %) patients used vitamin A; 30 (38 %) used vitamin D; and 22 (28 %) used vitamin K supplements. One patient originating from Canada reported the use of a CF-specific multivitamin supplement. In all cases the supplements were taken on prescription of the physician and most patients had used the supplements for an extended period of time. The percentage of PI patients reporting use of vitamin K for at least 5 years was 77 %; vitamins A and D, 96 %; and vitamin E, 98 %. Multivitamins were frequently used (42 % in PI group and 29 % in PS group) and were an important source of vitamins A, D, and E. Vitamin K content of multivitamin supplements ranged from 0 to 10 mg, and did not contribute significantly to overall intake.

Intake of fat-soluble vitamins from both single-nutrient and multivitamin supplements is reported for the PI group in Table II. Due to the low number of PS patients ($n = 14$), their data are not reported. For the PI group the mean (range) daily dose from both single-nutrient and multivitamin supplements was 400 (26–1212) μg/day of vitamin A, 5.0 (0.7–21.0) μg/day of vitamin D, 100 (5–600) mg/day of vitamin E, and 1.4 (0.3–10.0) mg/day of vitamin K (Table II).

Of those PI patients who reported the use of these vitamin supplements, only 9 % met the recommended dose for vitamin A, 32 % for vitamin D, 59 % for vitamin E, and 81 % for vitamin K (Figure 1a–d).

Table I. Characteristics of the study population and use of supplements (total and specific).

	Pancreatic-insufficient (n = 79)	Pancreatic-sufficient (n = 14)
Men (%)	56	43
Age (years), median (range)	25 (18–50)	32 (21–52)
Height (m), mean (SD)	1.72 (9.6)	1.74 (10.0)
Weight (kg), mean (SD)	62.0 (9.3)	71.5 (9.2)
BMI (kg/m^2), mean (SD)	21.0 (2.5)	23.6 (3.2)
Supplement use, total, n (%)	66 (84 %)	8 (57 %)
Supplement use, specific, n (%)		
Vitamin A	29 (37 %)	1 (7 %)
Vitamin D	30 (38 %)	2 (14 %)
Vitamin E	50 (63 %)	1 (7 %)
Vitamin K	22 (28 %)	1 (7 %)
Multivitamins	33 (42 %)	4 (29 %)
Vitamin C	22 (28 %)	1 (7 %)
Vitamin B-complex	8 (10 %)	1 (7 %)
Calcium	5 (6 %)	1 (7 %)
Iron	1 (1 %)	0 (0 %)
Other (e.g. magnesium and folic acid)	2 (3 %)	2 (14 %)

Table II. Use of fat-soluble vitamins in PI patients (n = 79) and recommended doses.

Vitamin	N* (%)	Median (range) daily dose from single nutrient and multivitamin supplements		Recommended dose of vitamin supplements**
Vitamin A	56 (71 %)	400 μg/day	(26–1212)	1200–3000 μg/day
Vitamin D	57 (72 %)	5.0 μg/day	(0.7–21.0)	10–20 μg/day
Vitamin E	61 (77 %)	100 mg/day	(5–600)	100–400 mg/day
Vitamin K	26 (33 %)	1.4 mg/day	(0.3–10.0)	1 mg/d to 10 mg/wk

* Patients using the vitamin either as a single nutrient supplement or in the form of a multivitamin
** Based on European guidelines [8].

Use of other vitamins, minerals and other supplements

The use of other vitamins, minerals, and other supplements is reported in Table I. Multivitamins were most often used and in 44 % this use was undertaken on the patient's own initiative. Nine patients used a vitamin B-complex and 8 of them reported that this was advised by their physician. Calcium supplements were taken by 6 patients and 4 of them reported that this was advised by their physician. Daily calcium intake from all supplements (including multi supplements) was 40–1060 mg/day with a mean of 153 mg/day. Only 1 patient took an iron supplement (prescribed, daily dose 210 mg/day). Other nutritional supplements that were reported by the patients were garlic supplements (2 patients), wheat germ oil (1 patient), protein powder (1 patient), and whey amino acids (1 patient). None of the patients reported the use of fish-oil supplements.

Serum concentrations of vitamin D and E

Serum 25-hydroxyvitamin D levels were available for 41 PI patients and 29 of them used supplemental vitamin D. Serum 25-hydroxyvitamin D ranged from 14

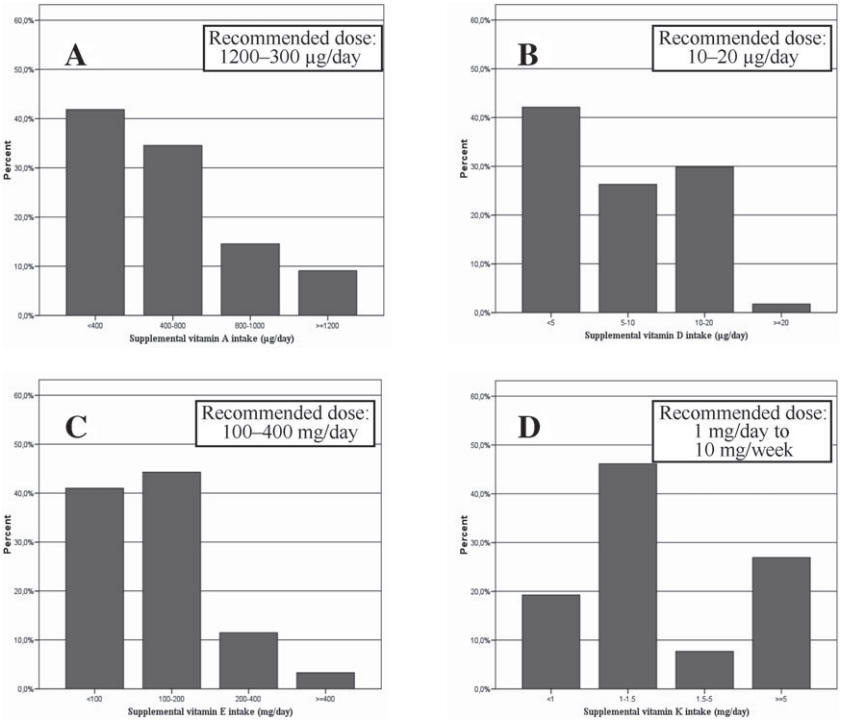

Figure 1: Intake of fat-soluble vitamins from supplements in PI patients reporting use of the specific supplements. A. Vitamin A (n= 56); B. Vitamin D (n = 57); C. Vitamin E (n = 61); D. Vitamin K (n = 26).

to 86 nmol/L with a mean of 37 nmol/L. Low vitamin D levels, i. e. < 27 nmol/L [17], were observed for 12 patients (= 29 %). Of these 12 patients, 4 did not use any vitamin D supplementation. Supplemental intake of vitamin D was not correlated with serum 25-hydroxyvitamin D levels (Figure 2 A, Pearson correlation coefficient = 0.22, p = 0.18). Serum concentrations of vitamin E were available for 39 PI patients; 28 of them used vitamin E supplements. Serum vitamin E ranged from 2 to 41 µmol/L, with a mean of 20.4 µmol/L. For 6 patients (15 %) low serum vitamin E levels were observed (i. e. < 12 µmol/L). Of these 6 patients, 3 did not use any vitamin E supplementation. No association was observed between intake from supplements and serum levels (Figure 2B, Pearson correlation coefficient = –0.09, p = 0.60).

Discussion

In this study we report the use of vitamin and mineral supplements in daily practice in adult CF patients. The majority of our study population (80 %) used vitamin and/or mineral supplements on a daily or weekly basis. However, 19 % of PI patients did not use any fat-soluble vitamins, despite the CF Center's protocol. As expected and in concordance with European guidelines [8], the use of fat-soluble vitamins was higher in PI patients compared to PS patients.

The self-reported use of the prescribed treatment with vitamin A (71 %), vitamin D (72 %), and vitamin E (77 %) in the PI patients is slightly higher than observed in a study in the UK, in which 62 % reported to always or usually take prescribed vitamins [14]. In a study from the USA, a higher percentage (88 %) of compliance was observed with the use of a CF-specific multivitamin supplement [15]. Our study showed that the use of vitamin K was the lowest of all fat-soluble vitamins (28 %). However, this percentage is higher than the use described in a UK study in which only 18 % of patients routinely used supplemental vitamin K [12]. In the Netherlands vitamin K and E are given as separate supplements and vitamin K is mostly prescribed in the case of severe malnutrition or liver insufficiency. Vitamin K status is of importance as it has been shown that suboptimal status has been associated with decreased bone mass and abnormal bone biomarkers in CF [7]. Lack of reimbursement by health insurance may contribute to inadequate use of supplemental vitamins.

Our results show furthermore that a high percentage of patients that do report the use of supplements take doses that are below the recommended intake values. Reasons for this observation are unclear. It is possible that the majority of the patients used the vitamins for longer than 5 years and no adaptations were made over time to accommodate changing recommendations. Another possibility could be that patients prefer to take multivitamins, which coast less and also contain lower doses of fat-soluble vitamins than single-nutrient supplements. The intake of multivitamins in 42 % of the PI patients was higher than expected but slightly lower than that reported by Gordon *et al.* (52 %) [15]. There are no other studies that provide data describing on doses from multivitamins or single-nutrient supplements.

In this study, other nutritional supplements were rarely used. Calcium was only used as a single-nutrient

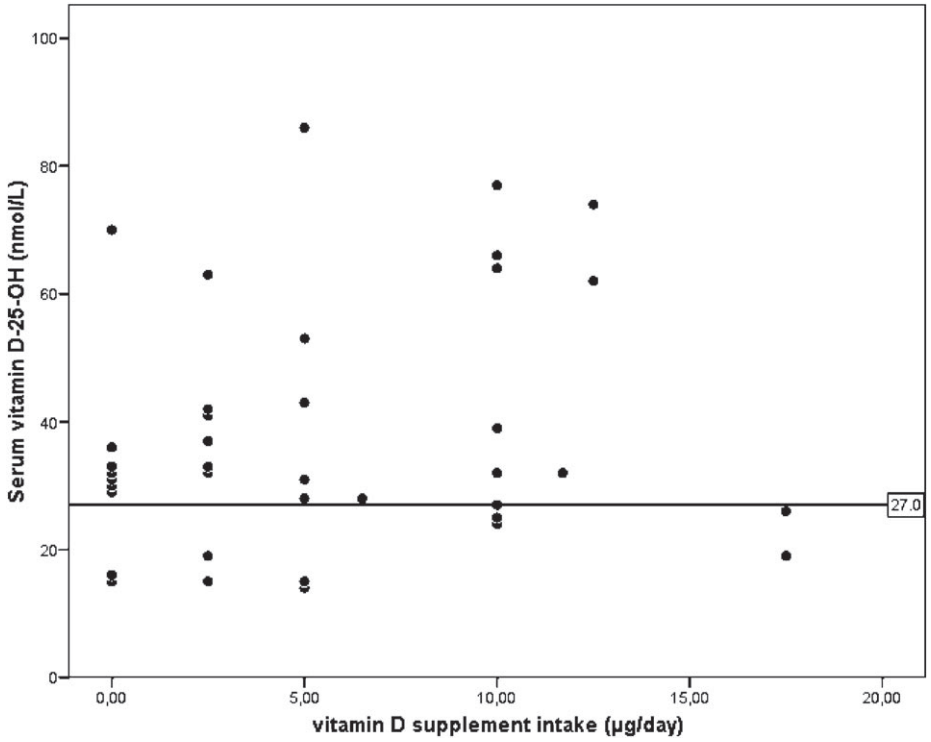

Figure 2a: Relation between supplemental vitamin D and serum 25-hydroxyvitamin D in 41 PI patients for whom serum con-centrations were available. The horizontal lines represent the reference value for serum 25-hydroxyvitamin D.

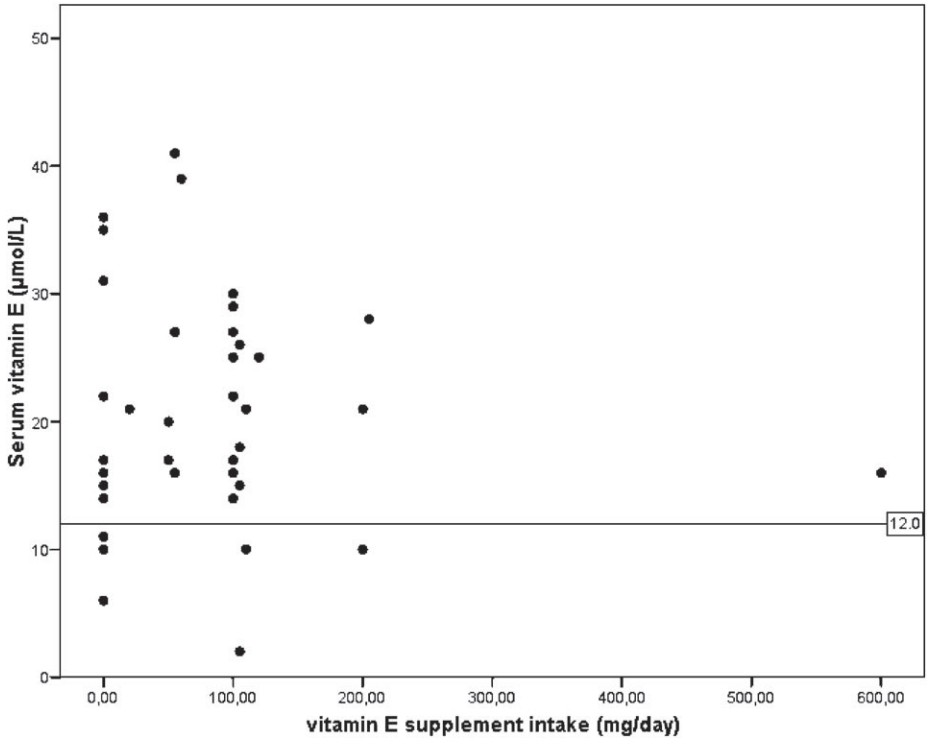

Figure 2b: Relation between supplemental vitamin E and serum vitamin E in 39 PI patients for whom serum concentrations were available. The horizontal lines represent the reference value for serum vitamin E.

supplement by 6 of 93 patients (6 %), which is much lower than the 25 % usage described by Gordon [15]. The combined usage of multivitamins containing calcium increased the total amount of calcium intake.

None of the patients reported the use of omega-3 fatty acids, which was unexpected because of the current attention given to the potential positive effects of this supplement [18].

Limitations of this study should be acknowledged: the data that presented are self-reported numbers of use of a wide range of supplements; actual prescription information for each patient is not available.

Data for fat-soluble vitamin levels in serum are incomplete, limiting the ability to draw strong conclusions. We did not observe an association between intake of vitamin D from supplements and serum 25-hydroxyvitamin D, which is in agreement with findings of another cross-sectional study [19,20]. It has been suggested that low serum values are difficult to adjust with vitamin D supplements [21]. Season notably affects vitamin D levels [4]. Unfortunately, in our study, the time of the year in which vitamin D was measured was not the same for all patients, as it depended on the time of the annual check-up. Other factors such as dietary intake, type of vitamin D supplement, severity of disease, and exposure to sunlight are also important determinants [22, 23]. Only a few foods contain vitamin D (e.g., fish, dairy, meat, margarine) and it would have been interesting to include dietary intake of vitamin D. However, in the study of Gordon *et al.*, dietary vitamin D intake was not associated with serum vitamin D [15]. In our study population a lower percentage of patients was found to be vitamin D- deficient compared to the study population described by Gordon [15]. Compared to Feranchak, the prevalence of vitamin D and vitamin E deficiency was comparable for vitamin D (29 % versus 25 – 30 %) and much lower for vitamin E (15 % versus 95 %) [3].

No association was observed between vitamin E supplementation and serum concentrations. Probably supplemental vitamin E is not well absorbed when it is not taken with pancreatic enzymes, an observation also described by Feranchak [3]. In this study unfortunately, the intake of pancreatic enzymes combined with the fat-soluble vitamins was not investigated. Only the distribution of PI and PS patients was reported. It has been recommended to use, for the interpretation of adequate levels of the plasma, tocopherol/total lipid or cholesterol ratio as an index of vitamin E status, particularly when levels are low, because the vitamin E levels rise with lipids [8, 10]. Unfortunately these data are not available.

Another possible explanation for the lack of relation between serum values and supplemental vitamin use can be the dietary intake of the patients. The intake and influence of vitamin D- or E-enriched food supplements or the usual dietary intake of this study population was not assessed.

Conclusion

The majority of our study population reported the use of supplements. However, a high percentage of the PI patients use fat-soluble vitamins below recommended doses, especially for vitamin A and D. These results are in line with previous studies in the UK and USA. Fish oil capsules containing omega-3 fatty acids and other nutritional supplements were hardly ever used. Multivitamins are an important source to add in the total intake of vitamins and minerals. This study shows, despite the small amount of data, that the pancreatic-insufficient patient is at higher risk to develop deficiencies for fat- soluble vitamins despite supplementation. If these patients are not adequately monitored by physicians and dieticians and do not have appropriate supplementation, vitamin deficiencies may occur.

Abbreviations

PI	Pancreatic-insufficient
PS	Pancreatic-sufficient
CF	Cystic fibrosis

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