Dietary intake and body-growth in cystic fibrosis

J.W. Woestenenk

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Copromotor:

Dr. R.H.J. Houwen

... those having cystic fibrosis

unique

beautiful

vulnerable

like a rose petal ...

For Arne

For Rutger, Jort and Muriel

Contents

1

General introduction and outline of the thesis

Background

Cystic fibrosis (CF) is a life-threatening genetic disorder that affects mostly the lungs but also the pancreas, liver and intestine. CF is characterised by chronic pulmonary inflammation resulting in a gradual, progressive decline in pulmonary function.[1] The vast majority of CF patients also have an exocrine pancreatic insufficiency,[2] resulting in inadequate digestion and leading to fat malabsorption and malnutrition. Lung disease and nutritional status are tightly intertwined[3] and both are strong predictors of morbidity and mortality in patients with CF.[4-6]

Part 1: Dietary intake in children and adolescents with cystic fibrosis

Malnutrition in patients with CF can generally be managed by adequate caloric intake, although this might be difficult to achieve when patients have reduced appetite, infection-related anorexia, gastro-oesophageal reflux or abdominal pain.[1,5,7] In this respect, nutritional interventions can be helpful to enhance caloric intake. A systematic review of the literature on these interventions concluded that behavioural modification, oral supplementation, enteral tube feeding and parenteral nutrition were all successful.[8] However, this review was conducted in 1997 and, as the nutritional status of patients has improved during the last 15 years,[9,10] the effectiveness of nutritional interventions might have changed as well.

To support good nutritional status, CF-specific guidelines state that patients should attain a caloric intake between 110% and 200% of the gender- and age-specific estimated average requirement (EAR),[7,11] with appropriate fat intake.[1] However, it is questionable whether these recommendations are met, as studies of patients with CF indicate that their actual caloric intake is generally lower than the recommended EAR,[12-14] although it is still higher than the intake of healthy controls.[12,14]

Pancreatic enzyme supplementation in pancreatic insufficient CF patients will substantially reduce fat malabsorption and thus prevent malnutrition.[1,7] However, only few details are known about the daily practice of pancreatic enzyme replacement therapy (PERT) and the resulting coefficient of fat absorption (CFA) in large groups of patients with CF.[15,16]

Part 2: Body-growth in children and adolescents with cystic fibrosis

Lung disease and nutritional status are associated, and weight and height have a prognostic value for predicting pulmonary function,[17,18] although their long-term relationship is poorly understood because most studies have a follow-up period of 3 years or less.[19] In addition, height is largely genetically determined, depending on the height of the biological parents, and is also subject to the child's own developmental stage. Therefore, an approach taking into account the genetic potential, as well as the child's skeletal maturation, might be a more appropriate method to evaluate the height growth of a child with CF, especially because CF is associated with a delay in skeletal maturation.[20,21]

Part 3: Vitamin A and E intake in children and adolescents with cystic fibrosis

CF-specific guidelines recommend routine prescription of the vitamin A and E for all pancreatic insufficient patients to prevent a deficiency of these vitamins due to fat malabsorption.[1,7] It has also been suggested that an intake above the level that is needed to prevent a deficiency might be beneficial. However, this has been a subject of debate as studies have yielded conflicting results: some suggested that higher serum levels of both vitamin A[22-25] and E[23,24] could have protective effects on pulmonary function, whereas others found no protective effects whatsoever.[26-31] Moreover, the actual intake of both vitamin A and E in daily practice and the resulting serum levels are largely unknown.

Objective of this thesis

The aim of this thesis was to increase knowledge on the effectiveness of nutritional interventions; the daily practice of caloric, fat, vitamin A and E intake; and PERT, along with their relationship to either growth or pulmonary function in paediatric patients with CF. It also provides insight into caloric, fat, vitamin A and E intake, and PERT, compared to CF-specific recommendations.[1,7,11] Moreover, the use of height measurements, corrected for genetic potential and the bone maturation of children and adolescents with CF, was evaluated.

Outline of this thesis

Part 1: Dietary intake in children and adolescents with cystic fibrosis

Chapter 2 describes the results of a systematic review of the literature published after 1997 describing the effectiveness of nutritional interventions in patients with CF. Chapter 3 describes the actual dietary caloric and fat intake in a large cohort of children and adolescents with CF, and compares this to the intake of healthy controls. Chapter 4 records PERT and the CFA data during regular follow-up of a large cohort of paediatric pancreatic insufficient CF patients.

Part 2: Body growth in children and adolescents with cystic fibrosis

Chapter 5 describes the results of a retrospective study on weight, height and height-adjusted-for-target-height in a cohort of patients followed from the age of 2 to 10 years, and the relationship between these parameters and forced expiratory volume in 1 second, in children with CF at 6 years of age and older.

In Chapter 6, several methods for evaluating height growth in patients with CF are compared: height-for-age, height-for-bone-age, height-adjusted-for-target-height and height-for-bone-age-adjusted-for-target-height.

Part 3: Vitamin A and E intake in children and adolescents with cystic fibrosis

Chapter 7 is devoted to both vitamin A and E. Chapter 7.1 addresses the association between vitamin A intake, serum retinol levels, CFA and serum immunoglobulin G (IgG) levels, and Chapter 7.2 describes the longitudinal relationship of serum retinol and serum IgG on pulmonary function in children and adolescents with CF during a 7-year follow-up period. Subsequently, Chapter 7.3 is focused on both the association between vitamin E intake, CFA and IgG levels on α-tocopherol levels, and the longitudinal relationship of serum α-tocopherol and serum IgG on pulmonary function during a 7-year follow-up period.

In Chapter 8, the results are discussed and future directions for research are indicated.

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Part 1

Dietary intake in children and adolescents with cystic fibrosis

2

Nutritional intervention in patients with cystic fibrosis; a systematic review

J.W. Woestenenk [1]
S.J.A.M. Castelijns [2]
C.K. van der Ent [3]
R.H.J. Houwen [2]

[1] Internal Medicine and Dermatology, Dietetics and, Cystic Fibrosis Centre Utrecht, University Medical Centre Utrecht, Utrecht, the Netherlands.
[2] Department of Paediatric Gastroenterology, and Cystic Fibrosis Centre Utrecht, University Medical Centre Utrecht, Utrecht, the Netherlands.
[3] Department of Paediatric Pulmonology, and Cystic Fibrosis Centre Utrecht, University Medical Centre Utrecht, Utrecht, the Netherlands.

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Abstract

Aim

To systematically assess the literature published after 1997 describing the effectiveness of nutritional interventions in patients with cystic fibrosis.

Methods

An online search in PUBMED, EMBASE and COCHRANE databases was conducted. Original studies with 4 patients or more, describing a nutritional intervention and giving at least weight as an outcome variable, were included.

Results

The inclusion criteria were met by 17 articles, focusing on behavioural interventions (n = 6), oral supplementation (n = 4) or enteral tube feeding (n = 7). This latter intervention was universally successful to induce weight gain. One behavioural study and 2 oral supplementation studies also reported a significant weight gain.

Conclusion

Enteral tube feeding is effective to improve nutritional status, while the described effects of the behavioural intervention and the oral supplementation are not consistent at present.

Introduction

Cystic fibrosis (CF) is the most common lethal genetic disorder in Caucasians, affecting 1 in 4,750 live births.[1] It is characterised by a gradual decline in pulmonary function, intestinal malabsorption and often an impaired nutritional status. Lung disease and nutritional status are tightly intertwined[2] and both are strong predictors of morbidity and mortality in patients with CF.[1, 3, 4] Malnutrition, due to a negative energy balance, is a common problem caused by a combination of faecal fat losses and increased energy requirements due to the chronic infection.[5] Therefore, dietary guidelines prescribe that patients with CF should attain up to 200% of the recommended daily caloric intake.[6, 7] However, this can be difficult to achieve because patients may have reduced appetite, infection-related anorexia, gastro-oesophageal reflux or abdominal pain. In this respect, nutritional interventions can be helpful to increase caloric intake. In 1997, Jelalian et al. described in a meta-analysis that all nutritional interventions aimed at gaining weight were successful, including behavioural modifications, oral supplementation, enteral tube feeding as well as parenteral nutrition.[8] As CF treatment, and thus the nutritional status of patients has changed during the last 15 years,[9, 10] effectiveness of nutritional interventions might have changed as well. Therefore, we have conducted a systematic review of the literature published after 1997, describing the current effectiveness of interventions aimed at enhancing nutritional status in patients with CF.

Methods

An online search in PUBMED, EMBASE and COCHRANE Central Register of Controlled Trials was carried out for all available articles published from January 1st, 1997 up to April 30th, 2012. The search query was: 'cystic fibrosis' [MESH] AND 'diet' [MESH], 'cystic fibrosis' [MESH] AND ('body-size' [MESH] OR 'body-weight' [MESH]), 'cystic fibrosis' [MESH] AND ('gastrostomy' [MESH] OR 'enteral nutrition' [MESH]). With this latter search term also studies using (nasogastric) tube feeding were identified. The reference lists of eligible articles and review articles were examined for additional studies. Excluded were articles concerning animals, non-English or non-Dutch articles, editorials, reviews, meta-analyses, articles with no abstract available and articles with a minimal sample size of 3 subjects or less. The search yielded 361 articles which were screened on title and abstract, and considered suitable if a nutritional intervention, with the aim to improve weight in patients with CF, was described. Studies conducted in subgroups only, such as patients with CF-related diabetes, were excluded. This resulted in 119 publications that were potentially

eligible, which were subsequently screened on full text. To pass this final screening it was necessary that the clinical outcome included at least a weight variable, either absolute weight, z-score for weight, weight percentile, weight percentage, weight-for-height or body-mass-index (BMI), as a result of the treatment applied. Finally 17 articles were appropriate and included in this review. These studies described interventions involving behavioural modification aimed at increasing caloric intake, prescription of oral supplements or enteral tube feeding through a gastrostomy.

The following data were extracted: the name of the first author, country and year of publication, study design, the intervention offered for nutritional rehabilitation, duration of the intervention, size and, if available, gender and age distribution of the study population, initial weight, caloric intake, the duration of follow-up and, if described, pulmonary function assessed by forced expiratory volume in 1 second, expressed as percentage of predicted (FEV_1% pred.). The primary outcome measurement was the change in weight, either expressed as absolute weight in kilogramme, z-score for weight-for-age, weight percentile, percentage weight-for-age, percentage ideal-body-weight, percentage weight-for-height, absolute body-mass-index (BMI) in kg/m^2, percentage BMI or z-score for BMI. The secondary outcome measurement was the change in caloric intake per day and/or FEV_1% pred., if described.

Results

Nutritional interventions were subdivided into behavioural intervention (n = 6),[11-16] oral supplementation (n = 4)[17-20] and enteral tube feeding (n = 7).[21-27] The treatment length of the behavioural interventions ranged from 7 weeks[13-15] to 1 year[11] and the follow-up period from 1 year[11, 12, 16] to 2 years.[13-15] In 2 oral supplementation studies, the treatment length varied from 8 weeks[19] to 1 year.[18] In both, the follow-up started simultaneous with the introduction of the oral supplement and the duration was equal to the treatment length. The 2 other oral supplementation studies[17, 20] had both a treatment and follow-up period of 3 months. The follow-up of the enteral tube feeding interventions started simultaneous with the start of the tube feeding and lasted up to 4 years.[21, 24] The control groups were patients with CF who did not have the intervention,[11-18, 20, 22] or subjects served as their own control.[12, 19, 21, 23-27] Data are summarised in Tables 1, 2 and 3.

Sample characteristics of the nutritional intervention studies tended to be heterogeneous. The sample sizes varied from 7[13] to 102 subjects[18], and years of age ranged from 5 months[25] to 50

years.[21] Furthermore, the baseline nutritional status differed from well-nourished adult patients (BMI 21.0)[16] to severely malnourished paediatric patients (mean z-score for weight-for-age -3.05).[23] The primary outcome was weight gain. Changes in caloric intake per day and/or the FEV_1% pred. were described in 9[11-14, 17-20, 26] and 11 studies[14-18, 20-23, 25, 27], respectively.

Behavioural intervention studies

Design

Six behavioural intervention studies were included which differed in design.[11-16] The 'home-based' nutritional education program of Watson et al., focusing on well-nourished adults, was unique.[16] In this study, the intervention group received 10 learning modules which were designed to take 30 minutes per week and had to be completed at home. They also received a newsletter every 2 weeks, and 3 workshops at the clinic were organised: before, halfway and at the end of the home-based program. The intervention group was rewarded for making changes as well as for strengthening their behavioural changes. The control group received standard care. The follow-up measurements of anthropometry and pulmonary function took place 6 and 12 months after the end of the intervention. The other 5 studies focused on behavioural modification in children who in general had z-scores for weight indexes below 0 and above -1.[11-15] The first behavioural and nutritional intervention in the study of Powers et al. was conducted over a 1-year period in which families received 8 1-hour sessions which included nutritional counselling and behavioural management training.[11] This relatively small study (8 patients) served as pilot for a subsequent study conducted in 2005.[12] In the latter, parents were trained in effective child behavioural management skills, combined with individualised nutritional counselling that targeted increasing energy intake in 1 specific meal each week. The study was performed over an 8-week period and included a baseline study visit and 6 intervention sessions held in week 3 to 8. After these 8 weeks, the control group was able to cross over to the same intervention as given to the first intervention group to replicate the effect of the intervention. The 1-year follow-up assessments for anthropometric data took place every 3 months, and a diet diary was completed at 3 and 12 months follow-up.

In all 3 studies of Stark et al., both the parents and children in the intervention and control group were provided with the same nutritional information and caloric goals during 7-weekly sessions.[13-15] In the first 2 studies performed by Stark et al.,[13, 14] parents of the intervention group were instructed in behavioural management to motivate their child to eat, while the

children received behavioural training in meeting weekly caloric goals as well as a behavioural reward program. In the 2011 study[15] the intervention group consisted of the intervention group *and* the control group of the previous study of Stark et al., conducted in 2009.[14] This implied that the intervention group received either behavioural management instructions and nutritional counselling or nutritional counselling only. Pooling of both groups from the 2009 study into the 2011 intervention group was considered correct as no significant differences at 2-year follow-up were found between these 2 groups. Growth in the combined intervention group was compared with growth of CF patients receiving standard care during the same time period. This control group was randomly drawn from the US-CF registry. In all 3 studies the follow-up assessments for anthropometry, caloric intake and pulmonary function data took place at 6, 12 and 24 months and in both the 2009 and 2011 studies also at 3 and 18 month after the end of treatment.

Nutritional status

Watson et al.[16] and Powers et al. 2003[11] described no effects of the behavioural intervention on nutritional status. The intervention group in the study of Powers et al. 2005 had normal weight velocities[12] but no information was available on the control group because this group crossed over to the combined intervention group. Both the 2003 and 2009 studies of Stark et al. reported that the intervention group had gained more weight in comparison to the control group at initial evaluation points.[13, 14] However, after 2-years follow-up the intervention group had not gained more weight than the control group. The 2011 study of Stark et al. demonstrated a significant less decline in z-score for BMI between the combined intervention group and the control group that was randomly selected from the US-CF registry.[15]

Caloric intake

Four behavioural studies described the caloric intake per day.[11-15] In the pilot study of Powers et al. 2003, no significant differences were found in the caloric intake between the intervention group (behavioural intervention combined with nutritional counselling) and the control group (nutritional counselling only).[11] Nonetheless, in 2005 the same group found a significant improvement in caloric intake after 3 months and after 12 months in a group that received behavioural and nutritional counselling.[12] Similar results were found in the group who crossed over from the control group to the intervention group. In 2 studies of Stark et al., children receiving behavioural intervention combined with nutritional counselling increased

their daily caloric intake more than children who received nutritional counselling only,[13, 14] although this effect did not persist after a 2-year follow-up.[14]

Pulmonary function

Three behavioural studies described pulmonary function before and after the intervention.[14-16] No significant differences in pulmonary function were found before and after intervention, although in 1 study the decline in pulmonary function in the intervention group seemed to be slower than in the control group, although not significantly so.[15]

Table 1. Characteristics of behavioural studies.

First author, country, year of study, study design	Type of intervention	Context of intervention	Sample characteristics
Watson, UK, 2008[16] Randomised controlled trial Patients: I: 34 C: 34	Behavioural home-based nutritional education program vs. standard care Patients were treated	Treatment length: 10 weeks Follow-up: 1 y Outpatient	N = 68 / Male = 40 Mean age (y): I: 25.2 / C: 23.8 Nutritional status: BMI: I: 21.0 / C: 21.6 During follow-up 4 patients died, 12 defaulted from follow-up, 3 withdrawn from study and 1 moved.
Powers, US, 2003[11] Randomised controlled trial Patients: I: 4 C: 4 *pilot study*	Behavioural + nutritional counselling vs. nutritional counselling only Only parents treated	Treatment length: 1 y Outpatient	N = 8 / Male = ND Age: <3 y Nutritional status: % weight-for-age: 42
Powers, US 2005[12] Randomised controlled trial Patients: I: 4 / C: 6 Afterwards 5 patients from control group underwent behavioural + nutritional intervention to replicate the effects	Behavioural intervention combined with nutritional counselling vs. standard care Parents were treated	Treatment length: 8 weeks Follow-up: 1 y Outpatient	N = 10 Male = 6 Age (mo): 22 – 43 Mean age (mo): 31.5 ± 6.2 Nutritional status: z-score weight-for-age -0.19 ± 0.85

I = intervention group C = control group RDA = recommended daily allowances

Table 1. Continued.

Results growth parameters	**Caloric intake**	**FEV_1% predicted**
Baseline: weight (kg): I: 59.1 ± 9.7 C: 59.4 ± 10.0 // BMI: I: 21.0 / C: 21.6 After 6 mo: weight (kg): I: (n = 28): 59.5 ± 10.0 C: (n = 32): 60.2 ± 10.8 (p=0.13) After 12 mo: weight (kg): I: (n = 23): 59.9 ± 9.7 C: (n = 25): 60.6 ± 11.2 (p=0.18) BMI: I: 21.3 / C: 21.1 NS	ND	Baseline: I: 52.6 ± 25.3 C: 59.09 ± 22.3 After 6 mo: I: 54.9 ± 25.1 C: 59.9 ± 20.8 (p=0.576) After 12 mo: I: 52.8 ± 24.1 C: 58.3 ± 21.5 (p=0.621)
Baseline: % weight-for-age: I: 42.0 ± 13.9 / C: 16.7 ± 18.4 // weight (kg): I: 11.6 ± 1.3 / C: 10.1 ± 2.1 Post-treatment: % weight-for-age: I: 46.2 ± 8.2 / C: 21.5 ± 9.0 // weight (kg): I: 14.1 ± 1.9 / C: 12.8 ± 2.0 NS	Kcal/day // % RDA Baseline: I: 1020.6 ± 182.3 %RDA: 78.5 ± 14.0 C: 1030.8 ± 146.2 % RDA: C: 79.0 ± 11.2 Post-treatment: I: 1426.6 ± 284.2 % RDA: 109.7 ± 21.9 (p=0.07) C: 1316.2 ± 227.3 % RDA: 101.2 ± 17.5 NS	ND
Baseline: weight z-score: I: -0.30 ± 0.7 / C: 0.08 ± 1.0 After 12 mo (n = 9): weight gain velocity: I: 2.5 ± 0.96 kg / C: ND (for child of same age at 50th percentile for weight normal is 2 kg / 12 mo)	Kcal/day Baseline: I: 1393.1 ± 118 / C: 1387.3 ± 105 Post-treatment: I: 2235.1 ± 706 / C: 1256.0 ± 215 (p=0.011) Caloric intake increase: I: 842 / C: -131 After 3 mo (n = 7): 1990.3 ± 337 (p<0.001) Caloric intake increase: 672. After 12 mo (n = 8): 2068.5 ± 484 (p<0.001) / Caloric intake increase: 750 Second sample control group: 5 patients from control group crossed over to behavioural nutritional intervention: Baseline: 1258.7 ± 240 Post-treatment: 2151.5 ± 301 (p=0.03)	ND
p-values from original studies added when available	ND = not described	NS = not significant

Table 1. Characteristics of behavioural studies.

First author, country, year of study, study design	Type of intervention	Context of intervention	Sample characteristics
Watson, UK, 2008[16] Randomised controlled trial Patients: I: 34 C: 34	Behavioural home-based nutritional education program vs. standard care Patients were treated	Treatment length: 10 weeks Follow-up: 1 y Outpatient	N = 68 / Male = 40 Mean age (y): I: 25.2 / C: 23.8 Nutritional status: BMI: I: 21.0 / C: 21.6 During follow-up 4 patients died, 12 defaulted from follow-up, 3 withdrawn from study and 1 moved.
Powers, US, 2003[11] Randomised controlled trial Patients: I: 4 C: 4 *pilot study*	Behavioural + nutritional counselling vs. nutritional counselling only Parents were treated	Treatment length: 1 y Outpatient	N = 8 / Male = ND Age: <3 y Nutritional status: % weight-for-age: 42
Powers, US 2005[12] Randomised controlled trial Patients: I: 4 / C: 6 Afterwards 5 patients from control group get behavioural + nutritional intervention to replicate the effects	Behavioural intervention combined with nutritional counselling vs. standard care Parents were treated	Treatment length: 8 weeks Follow-up: 1 y Outpatient	N = 10 Male = 6 Age (mo): 22 – 43 Mean age (mo): 31.5 ± 6.2 Nutritional status: z-score weight-for-age -0.19 ± 0.85

I = intervention group C = control group RDA = recommended daily allowances

Table 1. Continued.

Results growth parameters	**Caloric intake**	**FEV_1% predicted**
Baseline weigh-for-age: 12th percentile, range 3rd – 27th percentiles Post-treatment: weight gain (kg): I: 1.48 / C: 0.78. After 6 mo: I: 3.45 / C: 1.45 After 12 mo: I: 5.23 / C: 2.97 After 24 mo: I: 7.57 / C: 7.32 Weight percentile: I: 2 of 3 increased, 1 stayed on 4th percentile / C: 2 of 4 declined, 1 stable, 1 increased.	Kcal/day Baseline increase: I: 1829 / C: 1806 Post-treatment increase: I: 1036 (± 401) / C: 408 (± 410) After 24 mo: I: mean 946 kcal above baseline C: mean 313 kcal above baseline	Baseline: mean 95% (range 75% – 145%)
Baseline weight (kg): I: 21.79 ± 6.44 / C: 22.62 ± 7.45 Z-score BMI: I: -0.77 ± 1.12 / C: -0.49 ± 0.71 Post-treatment: weight (kg): I: 23.26 ± 7.1 / C: 23.54 ± 7.78 // Weight changes (kg) I: 1.47 ± 1.27 / C: 0.55 ± 1.16 (p=0.01) Z-score BMI: I: -0.39 ± 1.08 / C: -0.31 ± 0.81 // BMI changes: I: 0.38 ± 0.46 / C: 0.20 ± 0.47 (p=0.03) After 24 mo (compared to pre-treatment): Weight (kg): I (n = 28): 28.51 ± 9.77 / C (n = 31): 29.51 ± 10.84 // Weight changes (kg): I: 6.97 ± 3.6 / C: 6.45 ± 3.67 NS. Z-score BMI: I: -0.56 ± 0.9 / C: -0.71 ± 0.66. BMI changes: I: 0.13 ± 0.81 / C: -0.22 ± 0.5 NS	Kcal/day Baseline: I: 1793 ± 350 / C: 1826 ± 476 Post-treatment: I: 2655 ± 553 / C: 2315 ± 549 Caloric intake increase: I: 872 ± 478 / C: 489 ± 314 (p<0.001) After 24 mo (compared to pre-treatment): I: (n = 26): 2523 ± 620 / C: (n = 25): 2411 ± 577 Caloric intake increase: I: 721 ± 522 / C: 533 ± 436 NS	Baseline: I: (n = 17): 88 ± 18 C: (n = 13): 92 ± 18 After 24 mo: I: (n = 18): 87 ± 18 C: (n = 15): 87 ± 17 NS
Baseline z-score BMI: I: -0.63 ± 0.94 / C: -0.47 ± 0.85 After 24 mo post-treatment: BMI z-score: I: -0.05 ± 0.68 / C: -0.21 ± 0.67 Decline in BMI z-score significantly less in I group (p<0.0001)	ND	Baseline: I: (n = 36): 89.95 ± 17.79 / C: (n = 173): 87.71 ± 20.16 After 24 mo post-treatment: I: 88.74 / C: 84.45 I: decrease 1.21 C: decrease 3.25 NS
p-values from original studies added when available	ND = not described	NS = not significant

Oral supplementation studies

Design

Included were 4 studies which investigated the effect of adding high energy supplements to the usual oral intake in patients with weight indexes z-scores below 0 and above -2[17-20] of which the children in the study of Poustie et al.[18] and Skypala et al.[19] had weight indexes above z-score -1. The supplement in each study was different, but aimed at either increasing energy intake by 20% or having an intake that was at least equivalent to the calculated energy requirements. In the study of Skypala et al. the children and adults acted as their own controls.[19] In the 4 weeks pre-treatment period they were monitored on their usual diet including oral supplements and overnight enteral tube feeds. In the 8-weeks intervention period, the overnight enteral tube feeds where continued while the oral supplements were replaced by the intervention supplement which was prescribed in a dose equivalent to a minimum of 20% of the patients' pre-trial energy intake. The intervention supplement was a flavoured powder which was not fortified which vitamins and minerals and, when reconstituted with 240 ml of full-fat milk, contained 2.0 kcal/ml. The anthropometric assessments took place during the intervention at week 0, 4 and 12. No further follow-up measurements were performed.

The children enrolled in the study of Steinkamp et al. were randomly allocated to a control group or to an intervention group.[20] During 3 months both the control group and the intervention group received dietary counselling while the intervention group achieved, additionally, an oral supplement with 1.0 kcal/ml consisting of 31% of energy from fat (half of which was linoleic acid), and 16% of energy from protein. Anthropometric, caloric and pulmonary function data were obtained after 3-months follow-up.

In the relative small study (13 patients) of Kalnins et al., a ready-to-use supplement with 1.5 kcal/ml, consisting of 30% of energy from fat and 20% of energy from protein was prescribed to children and adults, during a 3-month period with the aim to increase energy-intake by 20% of predicted energy needs.[17] The control group received dietary counselling in which it was advised to increase the energy intake by eating high caloric foods.

Anthropometry and pulmonary function were evaluated at the end of the intervention and after 3-months follow-up, the change in caloric intake only at the conclusion. In the 1-year study of Poustie et al., children were randomised into a group who had dietary counselling and oral supplements, and into a group who had dietary counselling only.[18] The nutritional facts of the prescribed oral supplements were heterogeneous but all aimed at increasing the energy intake by 20%. The assessments for anthropometric, caloric intake and pulmonary function data took place during the intervention at 3, 6 and 12 months.

Nutritional status

Two studies described a significant weight gain after intervention, either when comparing to the pre-intervention weight in the same group[19], or when compared to the weight of a control group without the intervention.[20] The other 2 studies did not find an effect on weight variables at the end of the intervention period.[17, 18]

Caloric intake

All 4 studies described the caloric intake. Apart from the study by Kalnins et al.[17] all showed a significant increase in caloric intake at the end of the intervention period.[18-20]

Pulmonary function

Three studies described the pulmonary function and in none of these studies significant differences in FEV_1% pred. were found between intervention and control groups, neither before nor after the intervention.[17, 18, 20]

Table 2. Characteristics oral supplementation studies.

First author, country, year of study, study design	Type of intervention	Context of intervention	Sample characteristics
Skypala, UK, 1998[19] Single group Controlled trial Patients: 26	Oral supplement: flavoured powder which has to be constructed with full-fatty milk (2 kcal/ml) Aim: increasing energy intake by 20% of the patients' pre-trail energy intake	Pre-treatment length: 4 weeks Treatment length: 8 weeks Outpatient	N = 26 / Male = 16 Mean age (y): 18.5 (9 – 34) Age ≤18 y (n = 15) Inclusion criteria: age <16 y: ideal weight-for-height <95% or recently a weight loss of 5% of their usual weight age >16 y: BMI less than 19
Steinkamp, Germany, 2000[20] Prospective randomised controlled trial I: 16 patients oral energy supplement + dietary counselling / C: 20 patients dietary counselling	Oral supplement: energy supplement (1.0 kcal/ml, 31 En% fat, 16 En% protein) Aim: optimise energy intake by closing the gap between calculated ideal and actual energy intake with supplement.	Treatment length: 3 mo Follow-up: 3 mo Outpatient	N = 36 / Male = 20 Mean age (y): I: 10.4 ± 4.3 C: 13.3 ± 3.8 Inclusion criteria: weight-for-height <95% of reference value
Kalnins, Canada, 2005[17] Randomised controlled trial I: 7 patients oral dietary supplement C: 6 patients dietary counselling	Oral supplement: energy supplement (1.5 kcal/ml) Aim: increasing energy intake by 20% of predicted energy need over a 3 mo period	Treatment length: 3 mo Follow-up: 3 mo Outpatient	N = 13 / Male = 3 Mean age (y) I: 19.5 ± 11.3 C: 16.4 ± 6.7 Inclusion criteria: ideal-body-weight <90% or 5% reduction in % ideal-body-weight in 3 mo

I = intervention group C = control group RDA = recommended daily allowances

Table 2. Continued.

Results growth parameters	**Caloric intake**	**FEV_1% predicted**
Pre-treatment: weight (kg): 43.8 (24.6 – 59.9) weight-for-height (% predicted): 90.6 Baseline, after 4 weeks pre-treatment weight (kg): 43.7 (26 – 59.6) weight-for-height (% predicted): 90.7 Week 12 (end of the intervention) weight (kg): 45.6 (27.7 – 59.3) (p<0.01) weight-for-height (% predicted): 94.8	Pre-treatment: 120% EAR After 12 weeks: 143% EAR (p<0.01)	ND
Baseline: weight (kg): I: 32.2 ± 8.9 / C: 27.3 ± 7.6 Weight-for-height (% predicted): I: 82.8 ± 8.6 / C: 87.8 ± 8.7 After 3 mo: weight (kg) I: 33.4 ± 9.6 (p<0.05) / C: 27.5 ± 7.5 Weight-for-height (% predicted) I: 84.8 ± 9.6 (p<0.01) C: 85.6 ± 10 (p<0.01)	Baseline (kcal/day): I: 2189 ± 731 C: 1881 ± 507 After 3 mo: I: 2733 ± 762 (p<0.01) C: 1928 ± 468	Baseline: I: 52 ± 22 C: 54 ± 25 After 3 mo: I: 51 ± 26 C: 53 ± 20 NS
Baseline: z-score weight-for-age: I: -1.2 ± 0.5 / C: -0.8 ± 0.8 % ideal-body-weight: I: 86 ± 8 / C: 83 ± 10 After 3 mo: z-score weight-for-age: I: -1.1 ± 0.7 / C: -0.7 ± 0.6 NS % ideal-body-weight: I: 85 ± 6 / C: 84 ± 13 NS After 6 mo: z-score weight-for-age: I: -1.3 ± 0.8 / C: -0.6 ± 0.9 NS % ideal-body-weight: I: 83 ± 6 / C: 83 ± 13 NS	Baseline (kcal/day): I: 2400 ± 600 C: 2800 ± 1100 After 3 mo: I: 2700 ± 700 C: 2800 ± 700 NS	Baseline: I: 66 ± 22 C: 62 ± 25 After 3 mo: I: 60 ± 26 C: 63 ± 16 NS After 6 mo: I: 62 ± 19 C: 66 ± 13 NS
p-values from original studies added when available	ND = not described	NS = not significant

Table 2. Characteristics of oral supplementation studies.

First author, country, year of study, study design	Type of intervention	Context of intervention	Sample characteristics
Poustie, UK, 2006[18] Randomised controlled trial I: 50 patients oral supplementation + dietary counselling / C: 52 patients single dietary counselling	Oral supplement: Oral protein energy supplement Aim: increasing energy intake by 20% of the patients' usual energy intake	Treatment length: 1 y Outpatient	N = 102 / Male = 54 Age (y): 2 – 15 Inclusion criteria: BMI between 0.4th and 25th percentiles, no weight loss in the previous 3 mo or 5% weight decrease within 6 mo

I = intervention group C = control group RDA = recommended daily allowances

Table 2. Continued.

Results growth parameters	**Caloric intake**	**FEV_1% predicted**
Baseline: BMI percentile: I: 34.27 ± 23.96 / C: 31.52 ± 25.36 Weight percentile: I: 25.07 ± 20.37 / C: 24.69 ± 22.79 Differences after 12 mo: BMI percentile: I: 0.67 ± 18.2 / C: -2.32 ± 9.63 NS Weight percentile: I: 0.83 ± 10.96 / C: -1.0 ± 7.14 NS	Baseline %EAR: I: 118.43 ± 28.71 C: 116.24 ± 29.59 Differences after 12 mo: I: 24.48 ± 22.87 C: 6.63 ± 25.21 (p=0.01)	Baseline: I: 81.34 ± 16.16 C: 73.67 ± 18.58 Differences after 12 mo: I: -3.41 ± 13.5 C: -1.50 ± 14.89 NS
p-values from original studies added when available	ND = not described	NS = not significant

Enteral tube feeding studies

Design

Seven studies on enteral tube feeding were included.[21-27] Four studies enrolled patients with weight indexes z-scores below -1,[21, 22, 24, 25] and 3 studies included malnourished patients (weight indexes z-scores below -2).[23, 26, 27] Each investigated the effect of overnight tube feeding given by gastrostomy, thus providing 25% – 60% of the recommended caloric intake. The study of Bradley et al. was unique as it was a pair-matched controlled study, while all other studies did not include a control group, but evaluated the effect of the intervention by comparing baseline weight indexes with the same variable after enteral tube feeding was implemented for some time.[22] Bradley et al. supplemented 18 children, who were enrolled over a 5-year span, with a whole-protein formula, 1 with a partially hydrolysed formula and 1 with an elemental formula. The anthropometric and pulmonary assessments took place at 6 and 12 months. Williams et al. enrolled both children and adults and prescribed a concentrated modular elemental feed combined with Polycose (up to 2.6 kcal/ml) to all pancreatic insufficient patients, and to sufficient patients a whole protein feeding (1.5 kcal/ml).[27] For both groups the enteral tube feeding provided 40% – 60% of the recommended daily advice, and at month 6 and 12 anthropometric and pulmonary function data were obtained. In the study of Truby et al., children were provided with enteral tube feeding containing 1.0 or 1.5 kcal/ml. Anthropometric and pulmonary function data were assessed 1 and 2 years after the start of the enteral tube feeding.[25] Both studies enrolled patients over a 6-year period. The children in the study of Van Biervliet et al. received 40% of the recommended daily advice by providing a high energy (1.5 kcal/ml) polymeric tube feeding.[26] They studied data of children from 2 years before and after the gastrostomy insertion, and evaluation of anthropometric data took place 3 and 6 months after the gastrostomy insertion. The time span of enrolment was not described. Efrati et al., Rosenfeld et al., and Best et al. investigated the effect of enteral tube feeding in children and adults, included over a period of 9-years, 13-years and 20-years, respectively.[21, 23, 24] The follow-up assessments for anthropometric data in the study of Efrati et al. took place after 6 – 12 months and 18 – 24 months while the other 2 studies assessed both anthropometric and pulmonary function data in various time periods during the 4-year follow-up.[21, 24] These last 3 studies did not mention the type of the enteral tube feeding prescribed.

Nutritional status

In the only study that included a control group, the intervention group significantly improved in z-scores for weight and BMI after 6 and 12 months of the start of enteral tube feeding.[22] Apart from the study by Williams et al.[27], who reported both absolute weight gain and z-score for BMI, the other studies reported percentiles, percentages or z-scores for weight variables. Also those studies including both children and adults[21, 23, 24, 27] reported separate data for adults and children.

In 5 studies, a significant improvement in the weight variables was found after the start of enteral tube feeding, with follow-up periods lasting from 1 year[26, 27] to 2 years[23] to 4 years.[21, 24] Although, Truby et al. described a significant weight gain after 1 year of enteral tube feeding, in the second year weight gains were less evident with no significant change in the weight indexes.[25]

Caloric intake

The caloric intake was only reported in the study of Van Biervliet et al.[26] In this study, patients improved their caloric intake with approximately 40% of the recommended daily intake after the start of the enteral tube feeding.

Pulmonary function

Five studies described the pulmonary function.[21-23, 25, 27] Stabilisation in pulmonary function in the intervention group after 6 and 12 months providing enteral tube feeding was found in the studies of Bradley et al.[22] and Williams et al.[27] Two studies demonstrated a gradual decline in pulmonary function, respectively from 71% FEV_1 pred. at baseline to 67% FEV_1 pred. after 1 year, and to 66% FEV_1 pred. after 2 years of gastrostomy feeding,[25] and from 44% FEV_1 pred. at baseline to 41% FEV_1 pred. after 1 year of gastrostomy feeding, and stabilizing at 41% FEV_1 pred. after 2 years.[23] Best et al. found a significant reduction in the rate of pulmonary decline after the start of enteral tube feeding in girls and in adult men (all $p<0.05$), while women showed a trend toward improvement.[21] For boys, no significant improvement in the decline of pulmonary function was found, but it should be noted that the initial rate of pulmonary function decline in boys was already low (-1.13%/y) in contrast to the initial rates of decline in other subgroups (from -4.32%/y to -8.59%/y), so an improvement might be more difficult to detect.

Table 3. Characteristics of enteral tube feeding studies.

First author, country, year of study, study design	Type of intervention	Context of intervention	Sample characteristics
Bradley, US, 2012[22] Retrospective controlled cohort study Patients: I: 20 C: 20	Overnight feeding, providing 50% of RDA	Follow-up: 1 y (simultaneous with start enteral tube feeding) Home-based Patients enrolled in a 5 y span	N = 40 Male: I: 8 / C: 8 Mean age (y): I: 9.0 ± 4.4 C: 9.1 ± 4.7 Nutritional status baseline: BMI <50th percentile
Williams, UK, 1999[27] Single group Pre-test – post-test Patients: 53 Patients acted as their own controls	Overnight feeding, providing 40 – 60% of RDA	Follow-up: 1 y (simultaneous with start enteral tube feeding) Home-based Patients enrolled in a 6 y span	N = 53 / Male = 14 Mean age (y): 22.0 ± 0.8 ≤18 y (n = 10; 4 boys): mean age (y): 14.7 ± 0.7 > 18 y (N= 43; 10 male): mean age (y): 23.7 ± 0.8 Nutritional status: BMI <17 Baseline weight z-score: ND During follow-up 16 patients died
Truby, Australia, 2009[25] Single group Pre-test – post-test Patients: 14 Patients acted as their own controls	Overnight feeding 5 - 7 days/week, providing 1/3 – 1/2 of estimated energy requirements	Follow-up: 2 y (simultaneous with start enteral tube feeding) Home-based Patients enrolled in a 6 y span	N = 14 M = 7 Age (y): 0.42 – 13 Mean age (y): 6.63
Van Biervliet, Belgium 2004[26] Single group Pre-test – post-test Patients: 11 patients Patients acted as their own controls	Overnight feeding, providing 40% of RDA	Follow-up: 2 y (simultaneous with start enteral tube feeding) Home-based	N = 11 Male = 3 Age (y): 0.6 – 14.8 Median age (y): 9.4 Nutritional status: weight-for-height <85% or z-score height <-2

I = intervention group C = control group RDA = recommended daily allowances

Table 3. Continued.

Results growth parameters	Caloric intake	FEV_1% predicted
Baseline: z-score weight-for-age: I: -1.40 ± 0.55 / C: -1.06 ± 0.74 (p=0.07) z-score BMI: I: -1.19 ± 0.6 / C: 1.10 ± 0.5 (p=0.1) After 6 mo: z-score weight-for-age: I: -0.73 ± 0.79 / C: -1.01 ± 0.76 (p<0.001) z-score BMI: I: -0.29 ± 0.84 / C: -1.02 ± 0.67 (p<0.001) After 12 mo: z-score weight-for-age: I: -0.76 ± 0.73 / C: -0.86 ± 0.70 (p=0.01) z-score BMI: I: -0.41 ± 0.76 C: -0.71 ± 0.51 (p=0.07)	ND	Baseline: I: (n = 14): 76.0 ± 19.5 C: (n = 13): 75.7 ± 19.0 (p=0.90) After 6 mo: I: 74.7 ± 22.0 C: 78.9 ± 24.0 (p=0.46) After 12 mo: I: 74.4 ± 21.4 C: 82.3 ± 22.9 (p=0.17)
Adults: baseline: weight (kg) 37.4 ± 0.8 / BMI: 14.9 ± 0.4 After 6 mo: weight (kg) (n = 37): 42.1 ± 1.1 (p=0.0001) BMI (n = 25): 17.7 ± 0.5 (p=0.0001) After 12 mo: weight (kg) (n = 22) 44.2 ± 1.3 (p=0.0001) BMI (n = 21): 17.7 ± 0.4 (p=0.0001) Children: baseline: weight (kg) (n = 10) 31.9 ± 2.7 After 6 mo: weight (kg) (n = 9): 35.3 ± 3.3 (p<0.02) After 12 mo: weight (kg) (n = 6) 35.1 ± 4.7 (p<0.02)	ND	Baseline: 21 (13 – 35) After 6 mo: 20 (13 – 35) After 12 mo: 22 (10 – 40) NS
Baseline: z-score weight-for-age: -1.20 ± 0.82 z-score BMI (n = 9): -1.13 ± 0.61 After 1 y: z-score weight-for-age: -1.05 ± 0.73 (p=0.475) z-score BMI (n = 9): -0.56 ± 0.62 (p=0.01) After 2 y: z-score weight-for-age: -1.15 ± 0.92 (p=0.546) z-score BMI (n = 9): -0.98 ± 1.01 (p=0.108)	ND	Baseline: (n = 7) 71.02 ± 13.53 After 1 y: 67.26 ± 17.54 (p=0.405) After 2 y: 66.28 ± 14.73 (p=0.498)
Baseline % weight-for-height: median: 81 (67 – 90) / z-score BMI: -2.34 (-2.95 – -1.29) After 3 mo (n = 7): % weight-for-height: > 90 z-score BMI -1.11 (-2.18 – 1.35) After 6 mo (n = 7): % weight-for-height: 91 (75 – 119) (p≤0.05) z-score BMI: -1.32 (-2.04 – 0.63) (p≤0.05)	Kcal/day before gastrostomy 940 – 2011 After start enteral tube feeding: 1027 – 2666 RDA by enteral tube feeding: 40% (14% – 90%)	NS

ND = not described NS = not significant

Table 3. Characteristics of enteral tube feeding studies.

First author, country, year of study, study design	Type of intervention	Context of intervention	Sample characteristics
Efrati, Israel, 2006[23] Single group Pre-test – post-test Patients: 21 Patients acted as their own controls	Overnight feeding, providing 40 – 60% of RDA	Follow-up: 2 y (simultaneous with start enteral tube feeding) Home-based Patients enrolled in a 9 y span	N = 21 / Male = 10 Age: 8 mo – 20 y Mean age: ND Nutritional status: % weight-for-height <85 or weight loss for more than 3 consecutive mo During follow-up 1 patient died
Rosenfeld, US, 1999[24] Single group Pre-test – post-test Patients: 21 Patients acted as their own controls	Overnight feeding, providing ¼ – ½ of estimated daily energy needs for CF patients	Follow-up: 4 y (simultaneous with start enteral tube feeding) Home-based Patients enrolled in a 13 y span	N = 21 Male = 7 Age (y): 1.1 - 20.8 Median age (y): 7.4 Weight <90% of ideal, linear stunting or failure to progress along baseline weight percentile for 3 to 6 mo

I = intervention group C = control group RDA = recommended daily allowances

Table 3. Continued.

Results growth parameters	**Caloric intake**	**FEV_1% predicted**
Baseline: z-score weight-for-age: -3.1 ± 1.4 z-score BMI: -2.1 ± 1.3 % ideal-body-weight: 84.6 ± 8.5 After 6 – 12 mo (n = 21): z-score weight-for-age: -2.5 ± 1.5 (p=0.013) z-score BMI: -1.2 ± 1.2 (p=0.001) % ideal-body-weight: 95.1 ± 12.9 ND After 18 – 24 mo (n = 14): z-score weight-for-age -2.6 ± 1.5 (p=0.026) z-score BMI: -1.27 ± 1.11 (p=0.006) % ideal-body-weight: 96.5 ± 11.1 (p=0.003)	ND	Baseline: (n = 16) 44.2 ± 13.9 (25 – 77) After 6 – 12 mo: (n = 15): 41 ± 13.3 (25 – 67) (p=0.05) After 18 – 24 mo: (n = 14) 41.4 ± 16.1 (16 – 65) trend toward improvement
Baseline (n = 21): median % ideal-body-weight: 89 (72 – 95) median weight: 2nd percentile (0.2 – 36) After 6 – 18 mo (n = 18): median % ideal-body-weight: 90 (85 – 99) (p≤0.002) median weight: 12th percentile (1 – 28) (p≤0.002) After 18 – 30 mo (n = 18): median % ideal-body-weight: 93 (86 – 98) (p≤0.002) median weight: 12th percentile (1 – 29) (p≤0.002) After 30 – 48 mo (n = 14): median % ideal-body-weight: 98 (94 – 107) (p=0.002) median weight: 19th percentile (1 – 31) (p=0.002)	ND	ND

ND = not described NS = not significant

Table 3. Characteristics of enteral tube feeding studies.

First author, country, year of study, study design	Type of intervention	Context of intervention	Sample characteristics
Best, US, 2011[21] Single group Pre-test – post-test Patients: 46 Patients acted as their own controls	ND	Follow-up: 4 y (2 y pre-treatment – 4 y post- treatment) Home-based Patients enrolled in a 20 y span	N = 46 Male = 28 Age (y): 5 – 50 Age at gastrostomy tube placement <18 y: (n = 33; 20 boys) mean age (y): 11 (5 – 15) ≥18 y: (n = 13; 8 men) mean age (y): 26 (18 – 50) Nutritional status baseline: Overall: BMI percentile: 13.3 <18 y: ND ≥18 y: BMI absolute: 18.2 During follow-up 4 patients died, 8 underwent lung transplantation

I = intervention group C = control group RDA = recommended daily allowances

Table 3. Continued.

Results growth parameters	Caloric intake	FEV_1% predicted
BMI percentile 2 y pre-treatment – 1 y post-treatment	ND	Slope before start
Overall (n = 46): from 13.3 to 19.1,		enteral tube feeding
median % BMI change: 6.3 (p=0.0007)		per year
Men (n = 8): median % BMI change: 4.6		Men: -5.91
(7 patients improved)		(p=0.0019)
Women (n = 5): median % BMI change: -8.3		Woman: -8.59
(1 patient improved)		(p=0.0001)
Boys (n = 20): median % BMI change: 8.3		Boys: -1.13
(16 patients improved)		(p=0.3453)
Girls (n = 13): median % BMI change: 7.1		Girls: -4.32
(12 patients improved)		(p=0.0055)
BMI percentile 2 y pre-treatment – 2 y post-treatment		Slope change after
Overall (n = 39): from 14.6 to 36.8,		start enteral tube
median % BMI change: 13.3 (p<0.0001)		feeding per year
Men (n = 5): median % BMI change: 9.0		Men: 5.01
(5 patients improved)		(p=0.0159)
Women (n = 3): median % BMI change: -5.0		Woman: 4.48
(1 patient improved)		(p=0.0712)
Boys (n = 19): median % BMI change: 14.0		Boys: 1.49
(15 patients improved)		(p=0.2297)
Girls (n = 12): median % BMI change: 16.0		Girls: 4.02
(10 patients improved)		(p=0.0107)
BMI percentile 2 y pre-treatment – 4 y post-treatment		
Overall (n = 29): from 14.5 to 26.0		
median % BMI change: 8.9 (p=0.0067)		
Men (n = 3): median % BMI change: 13.5		
(3 patients improved)		
Women (n = 1): median % BMI change: -20.7		
(0 patients improved)		
Boys (n = 15): median % BMI change: 6.8		
(8 patients improved)		
Girls (n = 10): median % BMI change: 14.1		
(8 patients improved)		

ND = not described NS = not significant

Discussion

This review demonstrates that in 1 out of the 6 behavioural studies a significant weight gain was found and in another study an increased caloric intake, although this was not reflected in weight gain. Oral supplementation proved to be successful in improving weight variables in 2 out of 4 studies, and in caloric intake in 3 out of 4 studies. No positive effects of behavioural interventions or oral supplementation on pulmonary function were described. In all studies, enteral tube feeding by gastrostomy results in significant weight gain and an overall trend towards a slower decline in pulmonary function in patients with CF.

The earlier meta-analyses by Jelalian et al. in 1997, included 4 behavioural, 6 oral supplementation, 5 enteral tube feeding and 3 parental nutrition studies, reported that all interventions were effective in inducing weight gain, with parenteral nutrition having the largest effect, then enteral nutrition, then oral supplementation while behavioural interventions had the smallest effect.[8] However, the difference in weight gain between the 4 types of intervention was not significant. As opposed to this earlier study, the current study did not find an improvement in weight for each nutritional intervention. This difference might be partly due to the small sample size of the studies analysed by Jelalian et al., which ranged from 3 to 15 patients, with a total number of 17 patients analysed for behavioural intervention, 56 for oral supplementation and 52 for enteral nutrition. This is less than the largest single centre study in each of these 3 groups in the current review. Moreover, the results of the meta-analysis represented only the effectiveness of half of the studies conducted because other studies were lacking data for an effect size calculation. The limited number of available studies could significantly affect the estimated effectiveness, and possible studies which were not effective in improving weight gain were excluded. Given the differences in sample size numbers and limited data analysed, it is conceivable that some of the findings by Jelalian et al. could not be replicated in the current review. In addition the nutritional status for the CF-population at large has been considerably improved since the meta-analysis by Jelalian was done, with, for example, a 7.8% gain in median BMI percentile between 2000 and 2010.[9] In the current CF population, with a better nutritional status, the effect of interventions which induce only marginal weight gain would be harder to detect. Especially conducted in patients who are only just below z-score 0 with respect to weight variables, such as in the behavioural intervention studies now analysed.

The generalizability of the results of studies analysed in this review was limited due to the heterogeneity of the intervention groups, with respect to years of age, nutritional status, caloric intake, pulmonary function and the duration of the studies. Firstly, the sample size varied widely, from 7[13] to 102 patients[18] while 6 out of 17 studies reviewed included less than 15 patients, respectively, 3 behavioural,[11-15] 1 oral supplementation[17] and 2 enteral tube feeding interventions.[25, 26] Secondly, the patients included in the reviewed studies had a large age range, varying from 5 months[25] to 50 years,[21] with nutritional intervention studies in children being overrepresented as 10 (5 behavioural[11-15], 2 oral supplemental[18, 20] and 3 enteral tube feeding interventions[22, 25, 26]) and 6 (2 oral supplemental[17, 19] and 4 tube feeding interventions[21, 23, 24, 27]) out of the 17 studies analysed enrolled children or both children and adults while 1 study (behavioural intervention[16]) included adults only. Although none of the studies demonstrated that specific age groups benefit from a particular intervention, the impact of years of age on treatment efficacy is not clear at present. Thirdly, the included patients varied in baseline weight from well-nourished[16] to malnourished.[23, 26, 27] Behavioural interventions were mainly conducted in patients with weight indexes above z-scores -1[11, 12, 14-16] while enteral tube feeding interventions were only done in patients with weight indexes below z-scores -1. Moreover, malnourished patients (weight index below z-scores -2) received only enteral tube feeding and no other type of intervention.[23, 26, 27] Therefore the effectiveness of behavioural interventions and/or oral supplementation in malnourished patients cannot be reviewed. Fourthly, respectively 8[15, 16, 21-25, 27] and 6 studies[11-13, 19, 24, 26] lacked data on caloric intake and/or pulmonary function, so the effect of the interventions on these variables could not be assessed consistently. Lastly, the study duration varied from 7 weeks in behavioural interventions[13-15] to 4 years in enteral tube feeding studies[21, 24] and the follow-up from 8 weeks in oral supplementation[19] to 4 years in enteral tube feeding studies.[21, 24]

It is also important to note that a single research group from the Cincinnati Children's Hospital Medical Centre was responsible for 5 out of the 6 behavioural intervention studies;[11-15] no independent confirmation of their results has been published so far. So the generalizability of their results is unclear at present. In addition, the intervention group enrolled in the study of Stark et al. 2011,[15] was the study group *and* control group of the study of Stark et al. 2009,[14] which approach was considered justified as no differences between both groups were found at final follow-up. The results of this combined intervention group were subsequently compared to a nationwide reference group randomly drawn from the US-CF

registry. This registry stored patient information from all centres, including non-specialised centres. However, patients from centres with a focus on CF-care often show better growth results than nationwide cohorts,[3, 28] so it is unclear whether the better growth described by Stark et al for the intervention group is not – partly – due to this effect.

Despite these limitations, some conclusions seem to emerge from the studies reviewed. Nutritional intervention seems especially effective when applied to severely malnourished patients (weight index z-scores below -2); in this patient group enteral tube feeding has proven to be successful, both to improve the nutritional status and to slow the decline in pulmonary function.[21, 23, 25] The studies included in this systematic review give less guidance for patients with weight indexes z-scores below -1 and above -2. In those patients enteral nutrition is also effective, at least during the first year.[20, 22, 24, 26] As this intervention is invasive, oral supplementation might be started initially, as the study of Steinkamp et al., conducted in patients with weight indexes below -1 and above -2, demonstrated both a significant weight improvement and an increase in caloric intake.[20] With respect to behavioural intervention in this patient group, only 1 study showed a trend in weight gain during the first year, but not at the end of the follow-up.[13] So it is not clear at present whether CF patients with z-scores for weight indexes below -1 and above -2 benefit from this intervention. In patients with weight indexes z-scores below 0 and above -1, as enrolled in the studies of Skypala et al. and Poustie et al., the addition of oral supplementation seems successful in improving weight[19] and/or increasing the caloric intake.[18] Only 1 behavioural intervention conducted in this patient group (Stark et al. 2009[14]) showed significant weight gain, but only at the end of the intervention, and not at final follow-up. In addition, 1 behavioural study (Powers et al. 2005[12]) described an increased caloric intake. So, to date it is unclear whether this intervention should be routinely implemented in CF patients with weight indexes below 0.

Nowadays, the nutritional support is an integral part of multidisciplinary care of patients with CF, supported by CF-specific guidelines.[6, 7] These guidelines provide recommendations for identifying patients at-risk for malnutrition as well as for those with actual malnutrition. In these groups early intervention is extremely important to prevent negative long-term effects, although it is not always clear at present which type of intervention is most appropriate. Future studies, which should include a control group receiving current best treatment[6, 7] might determine more precisely which patient groups may benefit most from behavioural

interventions and/or oral supplements. The behavioural and oral supplementation interventions described in this systematic review also were relatively short (maximally 1 year, mostly 3 months or less). As the aim for CF patients is to obtain a – near – normal nutritional status for their entire life time, future studies should have a longer intervention and follow-up period, so it will become clear whether the observed short term effects will persist over a longer period. Finally, as the ultimate goal for patients with CF is a slower decline of pulmonary function, studies investigating nutritional interventions should include pulmonary function variables. Ideally these goals would be attained in prospective randomised controlled trials designed to assess the effect of a behavioural or oral supplementation intervention in CF patients with z-scores for weight-for-age between 0 and -2, as for these interventions the effect is not sufficiently clear yet. Study duration should be at least 1 year, as is the follow-up, and outcome variables should include weight variables as well as FEV_1% pred.

Conclusion

The studies included in this systematic review give less guidance for the role of behavioural intervention and oral supplements. However, it can be concluded that enteral tube feeding is effective to improve the nutritional status, especially in malnourished patients, and to slow further pulmonary function decline in patients with cystic fibrosis.

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3

Dietary intake in children and adolescents with cystic fibrosis

J.W. Woestenenk [1]
S.J.A.M. Castelijns [2]
C.K. van der Ent [3]
R.H.J. Houwen [2]

[1] Internal Medicine and Dermatology, Dietetics and, Cystic Fibrosis Centre Utrecht, University Medical Centre Utrecht, Utrecht, the Netherlands.
[2] Department of Paediatric Gastroenterology, and Cystic Fibrosis Centre Utrecht, University Medical Centre Utrecht, Utrecht, the Netherlands.
[3] Department of Paediatric Pulmonology, and Cystic Fibrosis Centre Utrecht, University Medical Centre Utrecht, Utrecht, the Netherlands.

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Abstract

Background and aim

The recommendation for caloric intake in patients with CF is to attain an intake between 110% and 200% of the gender- and age-specific estimated average requirement (EAR), of which 35% – 40 energy% should be from fat. It is questionable whether the advice is met.

Methods

1,726 Completed 3-day dietary food records of 234 CF patients (111 girls) and 2,860 completed two non-consecutive 24-h dietary assessments of healthy controls (1,411 girls) were studied. The dietary intake in CF patients was compared with that of healthy controls by using independent sample *t* tests or Mann-Whitney test.

Results

Caloric intake in children with CF varied highly with years of age (88% – 127% EAR) and is below or in the lower range of the recommended 110% – 200% EAR. However, the absolute caloric intake in children with CF was significantly higher compared to controls at all ages. In addition, apart from boys aged 1 – 3 years, all CF children had a fat intake of 35% or more of the total energy intake. This fat intake was significantly higher than in controls, as was the consumption of saturated fat, the latter being well above 10% of the total energy intake.

Conclusion

Although patients with CF generally do not meet the EAR recommendations, they had a significantly higher caloric intake than controls. Moreover, fat intake in CF patients does generally meet recommendations, but this resulted in a considerable consumption of saturated fat; a reduction in the latter seems appropriate.

Introduction

Cystic fibrosis (CF) is a lethal genetic disorder, characterized by chronic pulmonary inflammation, resulting in a gradual decline in pulmonary function. Most patients have pancreatic insufficiency, giving intestinal malabsorption. Lung disease and nutritional status are tightly intertwined,[1] in which a good nutritional status contributes to an improved pulmonary function and survival.[2-4] Therefore, an intake between 110% and 200% of the gender- and age-specific estimated average requirement (EAR) is commonly advised[5, 6] with an appropriate dietary protein intake, and 35% – 40% of the energy derived from dietary fat.[7] However, studies in patients with CF indicate that the actual caloric intake is generally lower.[8-10] Nevertheless, 2 small studies suggest that, although below recommendations, patients with CF still had higher intakes than their healthy counterparts.[8, 10] We therefore set out to record the dietary intake of caloric, protein, fat and carbohydrates in a large cohort of paediatric CF patients, and compare this intake with the intake of healthy controls.

Methods

Study population

A dynamic cohort of Dutch children (born between 1988 and 2012) with proven CF and who received medical care at the CF-centre of the University Medical Centre Utrecht, were studied retrospectively. Each child was confirmed as having CF by a positive sweat test and/or the presence of 2 CF-mutations, as well as clinical signs of CF and/or a positive family history. Yearly, weight and height were measured during routine clinical care visit, and dietary data were collected through 3-day dietary food records in clinical stable patients. Thus, the study's database contained data regarding the clinical parameters, dietary intake and demographics of all children who received medical care for CF at the University Medical Centre Utrecht from 1988 until August 2012. This study included children and adolescents aged 2 years and older, who had at least 1 completed 3-day dietary food record and were using pancreatic enzyme replacement therapy at time of reporting. All patients or parents of the young patients provided written informed consent for the storage and analysis of their data. The study was performed in accordance with the guidelines of the medical ethics board of the University Medical Centre Utrecht.

For controls, data of 2 Dutch national food consumption surveys among the healthy Dutch population, starting out at age 2 years[11, 12] were used. These surveys included samples of Dutch children (aged 2 to 18 years) selected from representative consumer panels. Caloric,

protein, fat, saturated fat and carbohydrate intake, collected through either two non-consecutive 24-h dietary records (aged 2 – 6 years) or two non-consecutive 24-h dietary recalls (aged 7 to 18 years), and data on year of age, gender and ethnicity of children and adolescents till age 18 year were extracted.

Weight and height assessment

Weight was measured to the nearest 0.1 kg using a digital weight balance, and height was measured to the nearest 0.5 cm using a stadiometer (Holtain, Crymich, UK). Both weight and height were compared to reference values for Dutch children by converting the values to z-scores for weight-for-age, height-for-age and body-mass-index using specialised software (Growth analyser 4 RCT, 2010, Dutch Growth Foundation). For non-Dutch children, weight and height were compared to reference values for their nationality. Children with 1 Dutch parent were analysed using Dutch growth charts.

Dietary intake assessment

Yearly, all CF patients received written instructions on completing a 3-day dietary food record including a request to maintain the child's usual dietary intake. All food and beverages consumed were recorded in portion sizes or weights during 2 weekdays and 1 weekend-day whenever possible. Where weights were not specified, portion size weights were obtained from reference data.[13] Registered dieticians coded and analysed the food records according a standardised approach, using the Dutch Food Composition Table (2010) of the Dutch Nutrition Centre.[14] The nutrient composition, expressed as mean daily caloric intake along with the contribution of protein, dietary fat, saturated fat and carbohydrate, expressed as gram and as percentage of the total energy intake (En%), was calculated for each assessment. The protein intake was also expressed as gram protein/kg body-weight/day. The children were grouped into age cohorts for which the specific Dutch nutritional recommendations (EAR) are made: 1 – 3 years, 4 – 8 years, 9 – 13 years and 14 –18 years, and subdivided into girls and boys.[15] For those who completed more than 1 3-day dietary food record during a specific age interval, a weighted mean intake was calculated. As this customary grouping gave less detailed results we subsequently expressed intake for each year of age for both girls and boys.

Statistics

Descriptive statistics of categorical variables were examined. For children with CF, the mean ± standard deviation of weight, height, and body-mass-index is presented. Age groups with less than 30 measurements were tested for normality. Children with CF and controls, both subdivided according to age group and to year of age, were compared with respect to energy intake, expressed as absolute caloric intake and %EAR, and absolute protein, fat, saturated fat and carbohydrate intake as well as their contribution to total caloric intake, by using independent sample *t* tests or Mann-Whitney test. Statistical analyses were performed using the Statistical Package for the Social Sciences Computer Software (SPSS Inc., version 20, IBM, Chicago, IL). All of the values were considered significant at $p<0.05$.

Results

Clinical characteristics

Data of 234 patients (97% Caucasian, 111 girls), were analysed. Overall, the mean z-scores for weight-for-age and height-for-age varied within the different age groups from -0.0 to -0.6 and from -0.2 to -1.0. Z-scores for body-mass-index varied between -0.3 and 0.4, in which the lower z-scores for both weight-for-age and height-for-age were reflected in relative better outcomes of the z-score for body-mass-index (see Supplemental Table 1a and 1b for details). In the CF group, a total of 1,726 3-day dietary food records were obtained. The control group consisted of 2,860 healthy children (1411 girls) who all completed two 24-h dietary assessments.

Caloric intake

Table 1a and 1b show data of the dietary intake in the different age groups for girls and boys. The commonly recommended caloric intake of 120% EAR was only met in children with CF up to 8 years of age. In the healthy control group, aged 1 – 3 years and 4 – 8 years, the intake also exceeded the EAR, while the intake was below the EAR in the older age groups. However, for each age group the absolute caloric intake and %EAR in CF children was significantly higher than in controls, with the difference between CF patients and controls increasing with year of age (Figure 1). Within the different EAR age groups, children at the beginning of an age category had a relatively low %EAR, with the %EAR increasing throughout the age group, and falling again at the beginning of the next age group (Figure 2, Supplemental Table 1a and 1b). This phenomenon is caused by the relatively large age groups

that are customary used in recommendations for dietary intake, encompassing children with hugely different weights and thus caloric needs. E.g. a 4-year old Dutch girl with CF has a mean weight of 17 kg, while an 8-year old girl with CF has a mean weight of 27 kg; yet for both girls the same recommendation applies.

Nutritional components

Children with CF as well as their controls obtained 12 En% – 14 En% of the total caloric intake from protein. From age group 4 – 8 years, the absolute protein intake in children with CF was higher compared to healthy controls. Moreover, apart from girls, age group 1 – 3 years, children with CF had significantly higher protein intake, expressed as gram protein/kg body-weight/day (Table 1a and 1b, and Supplemental Table 1a and 1b).

In all age groups, children with CF had significantly higher fat and saturated fat intakes compared to controls. The actual contribution of fat to the total caloric intake was 34 En% – 36 En% fat in children with CF, and 29 En% – 34 En% in the healthy counterparts, which was, apart from the age group 14 – 18 years, significantly different. Moreover, girls with CF derived more En% out of saturated fat until age group 14 – 18 years, while boys with CF in all age groups had a higher contribution of saturated fat to total caloric intake than their counterparts (Table 1a and 1b, and Supplemental Table 1a and 1b).

Both children with CF and their controls obtained between 51 En% and 59 En% of the total caloric intake from carbohydrates in which in children with CF generally a higher intake was found, although the contribution to total caloric intake was on average higher in healthy controls (Table 1a and 1b, and Supplemental Table 1a and 1b).

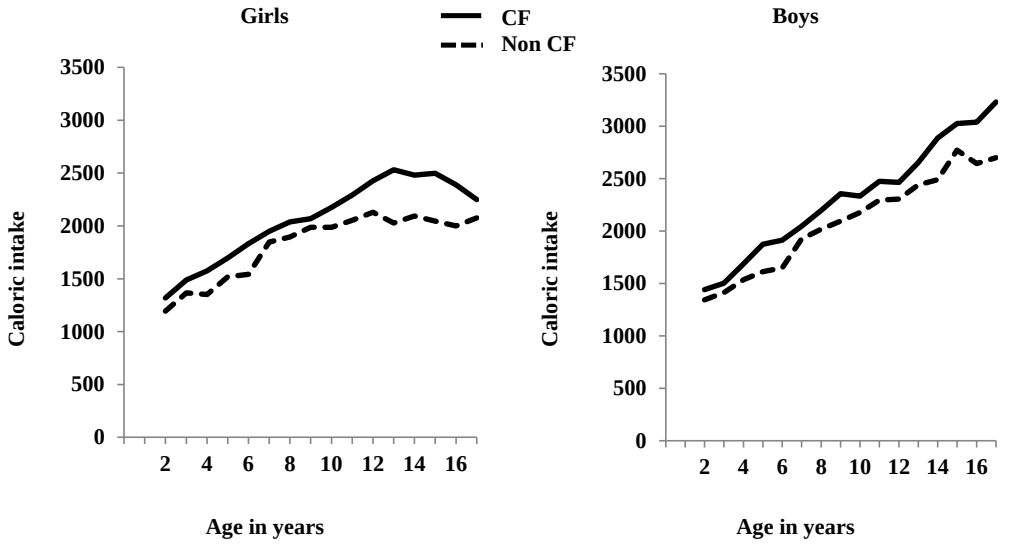

Figure 1. Mean caloric intake expressed as kilocalorie per age year and gender, derived from 1,726 3-day food records of 234 patients with CF (111 girls) and 2,860 two non-consecutive 24-h dietary assessments (1,411 girls) of healthy controls.

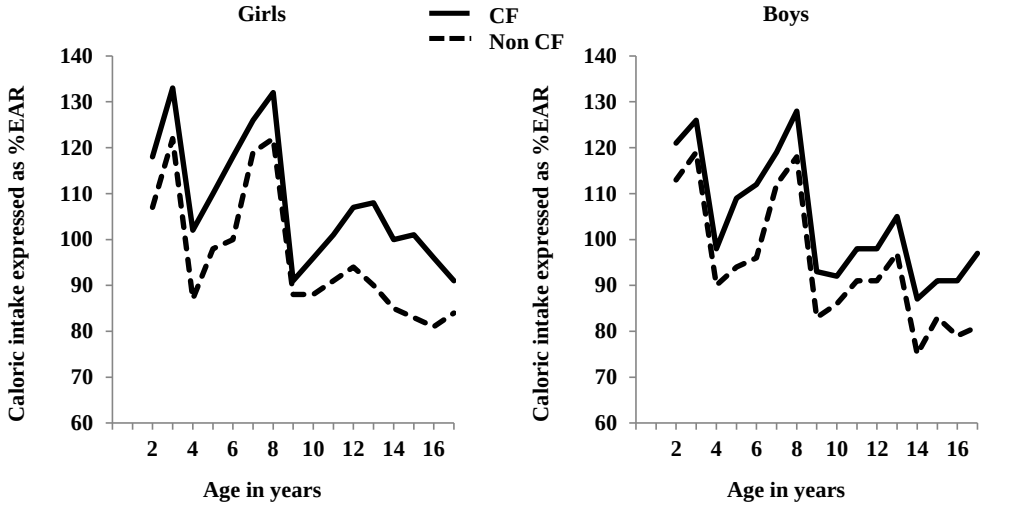

Figure 2. Mean caloric intake expressed as % estimated average requirement (EAR) per age year and gender, derived from 1,726 3-day food records of 234 patients with CF (111 girls) and 2,860 two non-consecutive 24-h dietary assessments (1,411 girls) of healthy controls.

Table 1a. Dietary intake derived from 811 completed 3-day dietary food records of 111 girls with CF (aged 2 – 18 years) and 1,411 completed two non-consecutive 24-h dietary assessments of healthy girls.

Age group	**1 – 3 years**			**4 – 8 years**		
	CF	Control	*p*	CF	Control	*p*
N	67	309		93	467	
Mean age, year ± SD	3.1 ± 0.4	3.0 ± 0.6	0.19	6.5 ± 1.0	6.3 ± 1.4	0.17
Dutch EAR kcal intake	1,119			1,548		
Kcal/day ± SD	1,419 ± 240	1,282 ± 292	0.00	1,848 ± 328	1,602 ± 383	0.00
%EAR ± SD	127 ± 21	115 ± 26	0.00	119 ± 21	104 ± 25	0.00
Protein, g/day ± SD	45 ± 11	43 ± 11	0.17	59 ± 12	51 ± 15	0.00
Protein, g/kg weight ± SD	3.1 ± 0.7	2.9 ± 0.8	0.15	2.7 ± 0.5	2.2 ± 0.6	0.00
Fat, g/day ± SD	55 ± 13	42 ± 14	0.00	72 ± 15	57 ± 20	0.00
Saturated fat, g/day ± SD	22 ± 7	16 ± 6	0.00	27 ± 9	22 ± 8	0.00
Carbohydrate, g/day ± SD	185 ± 36	183 ± 44	0.80	240 ± 52	218 ± 52	0.00
En% protein ± SD	13 ± 2	14 ± 2	0.01	13 ± 2	13 ± 3	0.63
En% fat ± SD	35 ± 5	29 ± 6	0.00	35 ± 5	32 ± 6	0.00
En% saturated fat ± SD	14 ± 4	11 ± 2	0.00	13 ± 4	12 ± 3	0.00
En% carbohydrate ± SD	53 ± 6	58 ± 6	0.00	53 ± 5	56 ± 7	0.00

Kcal = kilocalorie EAR = estimated average requirement SD = standard deviation

Table 1a. Continued.

Age group	**9 – 13 years**			**14 – 18 years**		
	CF	Control	*p*	CF	Control	*p*
N	81	350		42	285	
Mean age, year ± SD	11.2 ± 0.8	11.6 ± 1.4	0.04	15.3 ± 0.6	16.0 ± 1.2	0.00
Dutch EAR kcal intake	2,262			2,476		
Kcal/day ± SD	2,265 ± 368	2,038 ± 406	0.00	2,480 ± 432	2,057 ± 494	0.00
%EAR ± SD	100 ± 16	90 ± 18	0.00	100 ± 17	83 ± 20	0.00
Protein, g/day ± SD	75 ± 16	64 ± 18	0.00	89 ± 21	68 ± 18	0.00
Protein, g/kg weight ± SD	2.1 ± 0.5	1.6 ± 0.5	0.00	1.7 ± 0.5	1.2 ± 0.5	0.00
Fat, g/day ± SD	90 ± 19	77 ± 22	0.00	97 ± 27	77 ± 25	0.00
Saturated fat, g/day ± SD	34 ± 10	29 ± 9	0.00	36 ± 14	29 ± 10	0.00
Carbohydrate, g/day ± SD	289 ± 50	262 ± 58	0.00	313 ± 53	259 ± 68	0.00
En% protein ± SD	14 ± 2	13 ± 3	0.07	15 ± 2	14 ± 3	0.05
En% fat ± SD	36 ± 4	34 ± 6	0.02	35 ± 5	34 ± 6	0.20
En% saturated fat ± SD	13 ± 3	13 ± 3	0.06	13 ± 3	13 ± 3	0.11
En% carbohydrate ± SD	52 ± 5	52 ± 6	0.48	52 ± 6	51 ± 7	0.77

Table 1b. Dietary intake derived from 915 completed 3-day dietary food records of 123 boys with CF (aged 2 – 18 years) and 1,449 completed two non-consecutive 24-h dietary assessments of healthy boys.

Age group	**1 – 3 years**			**4 – 8 years**		
	CF	Control	*p*	CF	Control	*p*
N	59	317		102	489	
Mean age, year ± SD	3.1 ± 0.3	3.0 ± 0.6	0.48	6.8 ± 1.0	6.2 ± 1.4	0.00
Dutch EAR kcal intake	1,190			1,714		
Kcal/day ± SD	1,477 ± 281	1,379 ± 324	0.03	2,017 ± 350	1,713 ± 392	0.00
%EAR ± SD	124 ± 24	116 ± 27	0.03	118 ± 20	100 ± 23	0.00
Protein, g/day ± SD	46 ± 11	45 ± 13	0.58	63 ± 14	56 ± 16	0.00
Protein, g/kg weight ± SD	3.1 ± 0.7	2.9 ± 0.9	0.05	2.8 ± 0.5	2.4 ± 0.7	0.00
Fat, g/day ± SD	56 ± 15	46 ± 17	0.00	78 ± 17	60 ± 21	0.00
Saturated fat, g/day ± SD	22 ± 8	18 ± 17	0.00	29 ± 9	23 ± 8	0.00
Carbohydrate, g/day ± SD	196 ± 39	195 ± 45	0.95	264 ± 53	234 ± 52	0.00
En% protein ± SD	13 ± 2	13 ± 2	0.07	13 ± 2	13 ± 3	0.13
En% fat ± SD	34 ± 5	30 ± 6	0.00	35 ± 5	31 ± 6	0.00
En% saturated fat ± SD	14 ± 3	12 ± 3	0.00	13 ± 3	12 ± 3	0.00
En% carbohydrate ± SD	54 ± 6	58 ± 7	0.00	53 ± 5	56 ± 7	0.00

Kcal = kilocalorie EAR = estimated average requirement SD = standard deviation

Table 1b. Continued.

Age group	**9 – 13 years**			**14 – 18 years**		
	CF	Control	*p*	CF	Control	*p*
N	102	350		59	293	
Mean age, year ± SD	11.1 ± 0.9	11.5 ± 1.5	0.02	15.5 ± 0.7	16.0 ± 1.2	0.00
Dutch EAR kcal intake	2,524			3,330		
Kcal/day ± SD	2,422 ± 346	2,261 ± 520	0.00	2,956 ± 488	2,654 ± 819	0.01
%EAR ± SD	96 ± 14	90 ± 21	0.00	88 ± 15	80 ± 25	0.01
Protein, g/day ± SD	79 ± 14	73 ± 21	0.01	100 ± 20	87 ± 27	0.00
Protein, g/kg weight ± SD	2.2 ± 0.4	1.8 ± 0.6	0.00	1.8 ± 0.4	1.3 ± 0.4	0.00
Fat, g/day ± SD	96 ± 21	85 ± 28	0.00	116 ± 28	101 ± 40	0.01
Saturated fat, g/day ± SD	35 ± 11	32 ± 11	0.00	44 ± 13	37 ± 15	0.00
Carbohydrate, g/day ± SD	311 ± 51	291 ± 70	0.01	378 ± 65	327 ± 95	0.00
En% protein ± SD	13 ± 2	13 ± 3	0.74	14 ± 2	14 ± 3	0.59
En% fat ± SD	36 ± 5	34 ± 6	0.00	35 ± 5	34 ± 7	0.18
En% saturated fat ± SD	13 ± 3	13 ± 3	0.02	13 ± 3	12 ± 3	0.03
En% carbohydrate ± SD	52 ± 5	52 ± 6	0.73	52 ± 5	51 ± 7	0.16

Discussion

The current study showed that children and adolescents with CF had a caloric intake which is below or in the lower range of the recommended 110% – 200% EAR. It also showed a wide variability in intake expressed as %EAR within the different EAR age groups. However, the absolute caloric intake in children and adolescents with CF was significantly higher than in controls. In addition, in all age groups, children with CF had a significantly higher fat and saturated fat intake than controls.

This study found that the recommended intake for CF patients, to compensate for increased energy requirements due to malabsorption and chronic infections,[16] was only met in early childhood. Nevertheless, children with CF had a caloric intake that was up to 18% higher than their healthy counterparts, which is in line with previous relative small studies.[8, 10] It remains to be determined whether the higher intakes in CF patients are optimal, as we found that both weight and height in CF patients were slightly below average with outcomes between

-0.0 and -0.6 for z-score weight-for-age, and between -0.2 and -1.0 for z-score height-for-age. However, apart from an insufficient intake and/or malabsorption due to pancreatic insufficiency, this could also be caused by chronic inflammation[17] and/or the use of corticosteroids, which has a severe impact on linear growth.[18]

EAR is expected to cover a level of caloric intake that meets the requirement of half of the healthy population; in this study the actual intake in controls is above the EAR in the first 2 age groups, but falls below the EAR subsequently. Moreover, in the Netherlands,[15] as well as in several other countries, e.g. The USA,[19] and Germany, Austria and Switzerland who share common references,[20] the EAR has been set to age groups comprising 3 – 5 years, meaning that children of different ages share the same caloric recommendation. As a result, when a child reaches the first year of age of the next age group, he or she has to meet a significantly higher caloric intake overnight to achieve the EAR. As caloric requirements during childhood increase gradually each year, tailoring recommendations to 1-year age intervals instead of using large age groups, as was recently done in The United Kingdom,[21] might be more appropriate.

Children with CF, as well as controls derived 12 En% – 14 En% of the total caloric intake from protein, which added up to 1.8 g – 3.2 g protein/kg body-weight/day for children with CF and 1.2 g – 3.0 g protein/kg body-weight/day for healthy controls. This is far above the recommendations of respectively 5 En% – 8 En% and 0.8 g – 0.9 g protein/kg body-weight/day for healthy children over 1 year of age.[15] However, several short-term studies indeed suggest a favourable effect of high protein intake[22] or a high intake of essential amino acids on whole body-protein synthesis.[23] Although these finding have to be confirmed in long-term studies, the protein intake in our patients, that considerably exceeded recommendations, might in fact be of benefit to them.

Both boys and girls with CF derived or were close to achieving the recommended 35% of the caloric intake from fat, which is consistent with previous studies.[10, 24, 25] This higher fat intake, with respect to controls, was especially apparent in early childhood, probably due to the emphasis on a high fat diet directly after diagnosis. An adverse effect of this high fat intake is an excessive consumption of saturated fat, which was well above the advised limit of 10 En%, [15] as was also found in other studies.[24, 25] This might cause an increase in total and LDL-cholesterol[26] giving an increased risk of cardiovascular disease later in life, which becomes

relevant with the increasing survival in CF patients.[27] Indeed arterial stiffness, as a sign of premature atherosclerosis, was manifest in CF patients already during childhood[28] which was attributed to the systemic inflammatory state in CF patients,[28] although it is conceivable that the large amounts of dietary saturated fat intake also contributed. This additional risk can be limited by partly replacing dietary saturated fat by polyunsaturated fat, as the latter will cause a lowering in total and LDL-cholesterol in children,[29] and has the potential of slowing the development of atherosclerosis and thus decreases cardiovascular disease risk later in life.[30]

Several limitations of this study can be mentioned. Firstly, it is known that keeping food records can be burdensome, leading to alterations of the diet, over- and/or under-reporting and the accuracy might depend on the person who fills in the record. Moreover, portion size weights, obtained from reference data, may not accurately reflect the patients' intake. These limitations might affect the validity. Secondly, this study limited the extent of diversity in the study population by using group averages rather than individual averages. Thirdly, the possibilities to generalise the results are reduced by the single centre design as centre variability exists in terms of patient characteristics and therapy.

Conclusion

Children and adolescents with CF had a mean intake of 88% – 127% EAR, which is below or in the lower range of the recommended 110% – 200% EAR. However, they do have a significantly higher caloric intake compared to healthy controls. Therefore it seems more appropriate to use the actual intake in the healthy population as a starting point for nutritional advices in patients with CF, instead of EAR.

Moreover, patients with CF had a high dietary protein intake, both expressed as En% and as protein/kg body-weight/day, which might be beneficial. Additionally, CF children had a higher fat and saturated intake compared to healthy controls, especially in the younger age groups, which might give an increased risk for cardiovascular disease later in life. Therefore a reduction of saturated fat intake seems appropriate.

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Supplemental Table 1a. Caloric and macronutrient intake, expressed as mean ± standard deviation, derived from 811 completed 3-day dietary food records of 111 CF girls (aged 2 – 18 y) and 1,411 completed two non-consecutive 24-h dietary assessments of healthy control girls.

	CF				**Controls**		**CF**	**Controls**	
Age year	N	Weight kg z-score	Height cm z-score	BMI z-score	N	Dutch EAR caloric	Kcal ± SD %EAR ± SD	Kcal ± SD %EAR ± SD	*p*
2	45	13.1 ± 1.8 -0.4 ± 1.1	91.1 ± 5.4 -0.2 ± 1.2	15.8 ± 1.4 -0.2 ± 1.2	152	1119	1,319 ± 238 118 ± 21	1,194 ± 250 107 ± 22	0.00
3	60	16.0 ± 2.7 -0.1 ± 1.2	100.4 ± 6.1 -0.2 ± 1.3	15.8 ± 1.5 0.1 ± 1.1	157	1119	1,489 ± 247 133 ± 22	1,366 ± 306 122 ± 27	0.01
4	59	17.4 ± 2.6 -0.4 ± 1.2	106.5 ± 6.1 -0.4 ± 1.2	15.2 ± 1.3 -0.1 ± 1.0	103	1548	1,576 ± 267 102 ± 17	1,351 ± 282 87 ± 18	0.00
5	74	20.1 ± 3.4 -0.1 ± 1.3	113.9 ± 6.4 -0.3 ± 1.2	15.4 ± 1.3 0.1 ± 0.9	95	1548	1,696 ± 288 110 ± 19	1,519 ± 334 98 ± 22	0.00
6	57	22.4 ± 3.7 -0.1 ± 1.1	120.4 ± 5.9 -0.3 ± 1.1	15.4 ± 1.4 0.0 ± 0.9	114	1548	1,833 ± 355 118 ± 23	1,541 ± 326 100 ± 21	0.00
7	64	24.7 ± 3.9 -0.2 ± 1.1	125.8 ± 6.2 -0.4 ± 1.1	15.6 ± 1.4 0.0 ± 0.8	98	1548	1,950 ± 336 126 ± 22	1,848 ± 385 119 ± 25	0.09
8	67	27.1 ± 3.6 -0.3 ± 1.0	131.0 ± 6.1 -0.5 ± 1.0	15.8 ± 1.3 -0.0 ± 0.8	57	1548	2,039 ± 379 132 ± 24	1,895 ± 297 122 ± 19	0.02
9	63	30.0 ± 4.5 -0.3 ± 1.0	136.4 ± 6.9 -0.7 ± 1.1	16.1 ± 1.5 -0.1 ± 0.8	65	2262	2,067 ± 348 91 ± 15	1,988 ± 440 88 ± 19	0.27
10	59	32.9 ± 5.5 -0.4 ± 1.0	141.8 ± 7.0 -0.7 ± 1.0	16.3 ± 1.7 -0.3 ± 0.9	61	2262	2,174 ± 390 96 ± 17	1,987 ± 376 88 ± 16	0.01
11	64	37.2 ± 6.2 -0.4 ± 1.0	147.0 ± 7.6 -0.8 ± 1.1	17.1 ± 1.8 -0.1 ± 0.9	80	2262	2,292 ± 396 101 ± 17	2,052 ± 362 91 ± 16	0.00
12	51	41.9 ± 7.4 -0.4 ± 1.0	153.8 ± 7.2 -0.7 ± 1.0	17.0 ± 1.9 -0.2 ± 0.8	67	2262	2,426 ± 469 107 ± 21	2,130 ± 384 94 ± 17	0.00
13	48	46.2 ± 6.9 -0.5 ± 0.9	158.6 ± 7.4 -0.6 ± 1.1	18.3 ± 1.7 -0.1 ± 0.7	77	2262	2,530 ± 547 108 ± 21	2,027 ± 453 90 ± 20	0.00
14	40	50.2 ± 7.2 -0.5 ± 0.9	161.7 ± 6.9 -0.6 ± 1.0	19.1 ± 2.0 -0.0 ± 0.8	81	2476	2,480 ± 485 100 ± 16	2,093 ± 490 85 ± 20	0.00
15	30	52.9 ± 6.9 -0.6 ± 0.9	162.6 ± 6.4 -0.7 ± 1.0	20.0 ± 2.4 0.1 ± 0.9	64	2476	2,499 ± 444 101 ± 18	2,045 ± 469 83 ± 19	0.00
16	19	55.8 ± 7.3 -0.3 ± 1.0	162.1 ± 7.1 -1.0 ± 1.1	21.2 ± 2.2 0.4 ± 0.7	60	2476	2,389 ± 585 96 ± 24	1,999 ± 469 81 ± 19	0.00
17	11	56.3 ± 8.1 -0.3 ± 1.0	163.3 ± 6.4 -0.9 ± 1.0	21.1 ± 2.4 0.2 ± 0.8	80	2476	2,249 ± 598 91 ± 24	2,075 ± 538 84 ± 22	0.32

Kcal = kilocalorie EAR = estimated average requirement En% = percentage of energy

Supplemental Table 1a. Continued.

CF	Controls		CF	Controls		CF	Controls	
Protein gram ± SD En% ± SD / g/kg ± SD	Protein gram ± SD En% ± SD / g/kg ± SD	*p* gram En% / g/kg	Fat gram ± SD En% ± SD	Fat gram ± SD En% ± SD	*p* gram En%	CHO gram ± SD En% ± SD	CHO gram ± SD En% ± SD	*p* gram En%
42.0 ± 10.9	40.7 ± 10.4	0.46	51 ± 11	38 ± 13	0.00	173 ± 39	173 ± 37	0.92
13 ± 2 / 3.2 ± 0.7	14 ± 2 / 3.0 ± 0.8	0.01 / 0.42	35 ± 5	28 ± 6	0.00	53 ± 6	59 ± 7	0.00
47.5 ± 11.7	45.7 ± 12.0	0.32	58 ± 14	46 ± 14	0.00	192 ± 38	193 ± 47	0.90
13 ± 2 / 3.0 ± 0.8	14 ± 3 / 2.8 ± 0.8	0.05 / 0.09	35 ± 6	30 ± 5	0.00	53 ± 6	58 ± 6	0.00
49.2 ± 11.2	43.2 ± 11.9	0.00	59 ± 16	46 ± 13	0.00	210 ± 42	190 ± 48	0.01
13 ± 2 / 2.9 ± 0.7	13 ± 3 / 2.4 ± 0.7	0.41 / 0.00	34 ± 6	31 ± 6	0.01	54 ± 7	57 ± 7	0.02
54.8 ± 12.6	48.1 ± 12.0	0.00	66 ± 17	54 ± 18	0.00	219 ± 46	211 ± 45	0.26
13 ± 3 / 2.8 ± 0.7	13 ± 2 / 2.3 ± 0.6	0.54 / 0.00	35 ± 6	32 ± 6	0.00	52 ± 7	57 ± 6	0.00
58.0 ± 13.7	49.8 ± 14.1	0.00	72 ± 18	53 ± 18	0.00	237 ± 52	215 ± 46	0.01
13 ± 2 / 2.6 ± 0.7	13 ± 3 / 2.1 ± 0.6	0.41 / 0.00	36 ± 5	31 ± 6	0.00	52 ± 6	57 ± 7	0.00
62.5 ± 14.7	59.5 ± 16.4	0.25	77 ± 18	69 ± 21	0.01	250 ± 52	240 ± 54	0.26
13 ± 2 / 2.6 ± 0.6	13 ± 3 / 2.2 ± 0.6	0.72 / 0.00	36 ± 5	33 ± 6	0.01	52 ± 6	53 ± 7	0.38
65.4 ± 14.2	61.2 ± 14.3	0.10	81 ± 16	68 ± 18	0.00	263 ± 60	250 ± 45	0.20
13 ± 2 / 2.4 ± 0.5	13 ± 3 / 2.0 ± 0.5	0.71 / 0.00	36 ± 4	32 ± 6	0.00	52 ± 5	54 ± 7	0.13
69.5 ± 15.7	58.6 ± 17.7	0.00	81 ± 19	75 ± 26	0.14	264 ± 52	262 ± 55	0.83
14 ± 2 / 2.4 ± 0.6	12 ± 3 / 1.8 ± 0.6	0.00 / 0.00	35 ± 5	34 ± 6	0.09	52 ± 6	54 ± 6	0.04
74.6 ± 19.0	65.8 ± 15.9	0.01	87 ± 19	74 ± 22	0.00	273 ± 55	256 ± 51	0.09
14 ± 2 / 2.3 ± 0.7	14 ± 3 / 1.8 ± 0.6	0.55 / 0.00	36 ± 5	33 ± 6	0.00	51 ± 6	52 ± 6	0.17
78.3 ± 18.3	63.2 ± 15.9	0.00	92 ± 22	79 ± 20	0.00	287 ± 56	263 ± 57	0.01
14 ± 2 / 2.2 ± 0.6	13 ± 3 / 1.5 ± 0.4	0.00 / 0.00	36 ± 5	35 ± 6	0.12	51 ± 6	52 ± 6	0.26
80.3 ± 17.5	68.8 ± 19.3	0.00	97 ± 23	81 ± 23	0.00	308 ± 68	271 ± 56	0.00
13 ± 2 / 2.0 ± 0.5	13 ± 3 / 1.5 ± 0.5	0.53 / 0.00	36 ± 5	34 ± 6	0.08	52 ± 5	52 ± 6	0.77
84.3 ± 21.2	65.7 ± 20.7	0.00	102 ± 29	76 ± 22	0.00	318 ± 70	259 ± 66	0.00
14 ± 2 / 1.9 ± 0.5	13 ± 3 / 1.3 ± 0.4	0.35 / 0.00	36 ± 5	34 ± 6	0.06	51 ± 5	52 ± 7	0.53
88.1 ± 22.8	68.8 ± 20.0	0.00	96 ± 28	80 ± 25	0.00	314 ± 61	264 ± 67	0.00
14 ± 3 / 1.8 ± 0.6	14 ± 3 / 1.2 ± 0.4	0.11 / 0.00	35 ± 5	34 ± 6	0.54	52 ± 6	51 ± 6	0.79
91.5 ± 22.3	65.1 ± 15.9	0.00	99 ± 28	77 ± 28	0.00	312 ± 57	261 ± 61	0.00
15 ± 2 / 1.8 ± 0.6	13 ± 3 / 1.1 ± 0.3	0.00 / 0.00	36 ± 6	34 ± 6	0.19	51 ± 7	52 ± 6	0.40
83.4 ± 20.9	70.6 ± 18.8	0.01	86 ± 26	73 ± 23	0.04	321 ± 90	252 ± 69	0.00*
14 ± 3 / 1.5 ± 0.5	15 ± 3 / 1.2 ± 0.4	0.83 / 0.01	32 ± 6	33 ± 6	0.70	54 ± 6	51 ± 7	0.06
76.6 ± 18.2	67.7 ± 17.1	0.11	86 ± 36	78 ± 26	0.32	290 ± 65	258 ± 75	0.19
14 ± 3 / 1.4 ± 0.5	14 ± 3 / 1.1 ± 0.3	0.46 / 0.02	34 ± 5	34 ±6	0.99*	53 ± 4	51 ± 7	0.29

En% = percentage of energy g/kg = gram/kg body-weight/day CHO = carbohydrate * Mann-Whitney test

Supplemental Table 1b. Caloric and macronutrient intake, expressed as mean ± standard deviation, derived from 915 completed 3-day dietary food records of 123 CF boys (aged 2 – 18 y) and 1,449 completed two non-consecutive 24-h dietary assessments of healthy control boys.

	CF				**Controls**		**CF**	**Controls**	
Age year	N	Weight kg z-score	Height cm z-score	BMI z-score	N	Dutch EAR caloric	Kcal ± SD %EAR ± SD	Kcal ± SD %EAR ± SD	*p*
2	45	13.5 ± 1.7 -0.5 ± 1.1	91.6 ± 4.5 -0.4 ± 1.0	16.0 ± 1.2 -0.2 ± 1.0	159	1190	1,440 ± 327 121 ± 28	1,345 ± 328 113 ± 27	0.09
3	56	15.5 ± 1.6 -0.5 ± 0.9	99.1 ± 4.9 -0.6 ± 1.1	15.8 ± 1.1 -0.0 ± 1.0	158	1190	1,503 ± 263 126 ± 22	1,413 ± 318 119 ± 27	0.06
4	56	17.4 ± 1.9 -0.5 ± 1.0	106.7 ± 4.9 -0.6 ± 1.0	15.3 ± 0.8 -0.1 ± 0.7	123	1714	1,688 ± 296 98 ± 17	1,535 ± 335 90 ± 20	0.00
5	67	19.7 ± 2.2 -0.4 ± 0.9	114.0 ± 4.9 -0.5 ± 1.0	15.1 ± 1.0 -0.2 ± 0.9	109	1714	1,874 ± 280 109 ± 16	1,612 ± 300 94 ± 18	0.00
6	63	22.0 ± 2.4 -0.3 ± 0.9	119.8 ± 5.3 -0.6 ± 0.9	15.3 ± 1.0 -0.0 ± 0.8	101	1714	1,913 ± 329 112 ± 19	1,649 ± 337 96 ± 20	0.00
7	63	25.1 ± 2.9 -0.1 ± 0.9	126.1 ± 5.8 -0.6 ± 1.0	15.7 ± 1.2 0.2 ± 0.9	87	1714	2,046 ± 354 119 ± 21	1,925 ± 402 112 ± 23	0.06
8	76	27.5 ± 3.0 -0.2 ± 0.9	131.6 ± 5.4 -0.6 ± 0.9	15.9 ± 1.1 0.1 ± 0.8	69	1714	2,198 ± 381 128 ± 22	2,018 ± 393 118 ± 23	0.01
9	83	31.0 ± 3.7 -0.1 ± 0.9	138.3 ± 5.9 -0.4 ± 0.9	16.2 ± 1.4 0.1 ± 0.9	79	2524	2,357 ± 400 93 ± 16	2,096 ± 433 83 ± 17	0.00
10	78	33.9 ± 4.5 -0.1 ± 0.9	142.4 ± 5.8 -0.5 ± 0.8	16.7 ± 1.5 0.1 ± 0.9	60	2524	2,332 ± 379 92 ± 15	2,176 ± 462 86 ± 18	0.03
11	74	37.4 ± 4.7 -0.1 ± 0.8	148.0 ± 6.2 -0.5 ± 0.8	17.0 ± 1.5 -0.0 ± 0.8	73	2524	2,475 ± 433 98 ± 17	2,295 ± 466 91 ± 18	0.02
12	51	42.2 ± 6.4 -0.0 ± 0.9	155.2 ± 7.5 -0.4 ± 0.9	17.4 ± 1.7 -0.1 ± 0.9	68	2524	2,464 ± 498 98 ± 20	2,305 ± 633 91 ± 25	0.14
13	59	45.2 ± 7.0 -0.3 ± 0.9	159.7 ± 8.0 -0.6 ± 0.9	17.6 ± 1.7 -0.3 ± 0.9	70	2524	2,654 ± 458 105 ± 18	2,441 ± 534 97 ± 21	0.02
14	50	50.2 ± 7.2 -0.5 ± 0.9	161.7 ± 6.9 -0.6 ± 1.0	19.1 ± 2.0 -0.0 ± 0.8	70	3330	2,887 ± 475 87 ± 14	2,489 ± 702 75 ± 21	0.00
15	40	58.7 ± 8.2 -0.0 ± 0.9	173.3 ± 7.0 -0.4 ± 0.9	19.5 ± 2.0 -0.0 ± 0.9	75	3330	3,025 ± 521 91 ± 16	2,772 ± 741 83 ± 22	0.06
16	30	62.0 ± 7.5 -0.2 ± 0.9	176.0 ± 6.1 -0.6 ± 0.7	20.0 ± 1.9 -0.0 ± 1.0	71	3330	3,038 ± 643 91 ± 19	2,642 ± 946 79 ± 28	0.04
17	24	66.7 ± 5.5 -0.0 ± 0.6	178.9 ± 7.2 -0.3 ± 0.9	20.9 ± 1.7 0.2 ± 0.8	77	3330	3,231 ± 858 97 ± 26	2,699 ± 853 81 ± 26	0.01

Kcal = kilocalorie EAR = estimated average requirement En% = percentage of energy

Supplemental Table 1b. Continued.

CF	Controls		CF	Controls		CF	Controls	
Protein gram ± SD En% ± SD / g/kg ± SD	Protein gram ± SD En% ± SD / g/kg ± SD	*p* gram En% / g/kg	Fat gram ± SD En% ± SD	Fat gram ± SD En% ± SD	*p* gram En%	CHO gram ± SD En% ± SD	CHO gram ± SD En% ± SD	*p* gram En%
43.9 ± 10.1	44.9 ± 13.4	0.62	57 ± 19	44 ± 17	0.00	186 ± 42	191 ± 46	0.49
12 ± 2 / 3.3 ± 0.7	14 ± 3 / 3.2 ± 0.9	0.01 / 0.42	35 ± 6	30 ± 6	0.00	53 ± 6	58 ± 7	0.00
46.9 ± 11.5	45.4 ± 11.7	0.41	55 ± 13	48 ± 18	0.01	203 ± 39	199 ± 44	0.62
13 ± 2 / 3.0 ± 0.7	13 ± 2 / 2.7 ± 0.7	0.21 / 0.01	33 ± 5	30 ± 6	0.00	55 ± 5	58 ± 7	0.00
51.8 ± 11.9	49.7 ± 14.1	0.35	63 ± 15	52 ± 17	0.00	226 ± 48	217 ± 49	0.21
12 ± 2 / 3.0 ± 0.6	13 ± 2 / 2.6 ± 0.7	0.08 / 0.00	34 ± 6	30 ± 6	0.00	54 ± 6	58 ± 7	0.00
57.9 ± 12.4	53.8 ± 14.4	0.06	72 ± 14	56 ± 16	0.00	249 ± 49	222 ± 45	0.00
13 ± 2 / 2.9 ± 0.6	14 ± 3 / 2.5 ± 0.7	0.02 / 0.00	35 ± 6	31 ± 5	0.00	54 ± 6	56 ± 7	0.02
59.8 ± 14.1	54.0 ± 14.9	0.01	78 ± 19	57 ± 19	0.00	243 ± 47	229 ± 44	0.06
13 ± 2 / 2.7 ± 0.6	13 ± 3 / 2.3 ± 0.7	0.10 / 0.00	37 ± 6	31 ± 6	0.00	52 ± 6	57 ± 7	0.00
63.9 ± 15.1	60.8 ± 18.5	0.27	82 ± 22	69 ± 23	0.00	263 ± 52	257 ± 53	0.47
13 ± 2 / 2.6 ± 0.6	13 ± 3 / 2.3 ± 0.7	0.72 / 0.02	36 ± 7	32 ± 6	0.00	52 ± 7	55 ± 6	0.04
69.3 ± 15.8	64.4 ± 16.9	0.08	85 ± 21	75 ± 22	0.00	287 ± 62	263 ± 56	0.01
13 ± 2 / 2.5 ± 0.5	13 ± 3 / 2.1 ± 0.6	0.67 / 0.00	35 ± 6	33 ± 6	0.10	53 ± 7	53 ± 7	0.92
76.4 ± 17.4	67.5 ± 20.5	0.00	93 ± 24	77 ± 23	0.00	303 ± 58	273 ± 59	0.00
13 ± 2 / 2.5 ± 0.6	13 ± 3 / 2.1 ± 0.6	0.79 / 0.00	36 ± 6	33 ± 5	0.01	52 ± 6	53 ± 6	0.47
74.1 ± 16.6	69.0 ± 22.2	0.13	90 ± 22	81 ± 24	0.03	305 ± 61	282 ± 66	0.03
13 ± 2 / 2.2 ± 0.5	13 ± 3 / 1.9 ± 0.6	0.81 / 0.00	35 ± 6	34 ± 6	0.27	53 ± 6	53 ± 6	0.70
79.1 ± 16.0	74.7 ± 18.1	0.13	97 ± 28	87 ± 26	0.03	322 ± 59	294 ± 63	0.01
13 ± 2 / 2.1 ± 0.5	13 ± 3 / 1.8 ± 0.5	0.62 / 0.00	35 ± 6	34 ± 6	0.22	53 ± 6	52 ± 6	0.44
81.8 ± 17.3	74.6 ± 23.6	0.07	97 ± 27	89 ± 36	0.19	313 ± 62	290 ± 75	0.08
14 ± 2 / 2.0 ± 0.4	13 ± 3 / 1.7 ± 0.6	0.40 / 0.00	35 ± 5	35 ± 6	0.36	52 ± 4	52 ± 6	0.81
85.2 ± 19.0	78.4 ± 18.9	0.04	106 ± 22	91 ± 29	0.00	340 ± 75	316 ± 82	0.08
13 ± 2 / 1.9 ± 0.5	13 ± 3 / 1.6 ± 0.5	0.79 / 0.00	36 ± 5	34 ± 6	0.02	52 ± 6	52 ± 7	0.63
94.2 ± 20.7	80.2 ± 24.3	0.00	115 ± 29	93 ± 38	0.00	369 ± 63	321 ± 86	0.00
13 ± 2 / 1.8 ± 0.4	13 ± 3 / 1.4 ± 0.5	0.89 / 0.00	36 ± 5	33 ± 7	0.03	52 ± 6	53 ± 7	0.51
104.5 ± 26.0	85.2 ± 22.3	0.00	116 ± 27	111 ± 40	0.45	391 ± 83	345 ± 93	0.01
14 ± 3 / 1.8 ± 0.5	13 ± 3 / 1.4 ± 0.5	0.02 / 0.00	35 ± 5	36 ± 6	0.34	52 ± 6	51 ± 6	0.19
99.5 ± 24.6	91.0 ± 31.6	0.19	121 ± 35	99 ± 39	0.01	388 ± 86	319 ± 100	0.00
13 ± 2 / 1.6 ± 0.4	14 ± 3 / 1.3 ± 0.5	0.17 / 0.00	36 ± 5	34 ± 6	0.14	52 ± 6	50 ± 7	0.13
117.0 ± 36.7	90.5 ± 27.9	0.00	127 ± 48	101 ± 41	0.01	402 ± 96	324 ± 99	0.00
15 ± 2 / 1.8 ± 0.5	14 ± 3 / 1.3 ± 0.4	0.43 / 0.00	35 ± 7	34 ± 7	0.31	51 ± 7	49 ± 7	0.27

En% = percentage of energy g/kg = gram/kg body-weight/day CHO = carbohydrate

4

Pancreatic enzyme replacement therapy and coefficient of fat absorption in children and adolescents with cystic fibrosis

J.W. Woestenenk [1]
C.K. van der Ent [2]
R.H.J. Houwen [3]

[1] Internal Medicine and Dermatology, Dietetics and, Cystic Fibrosis Centre Utrecht, University Medical Centre Utrecht, Utrecht, the Netherlands.
[2] Department of Paediatric Pulmonology, and Cystic Fibrosis Centre Utrecht, University Medical Centre Utrecht, Utrecht, the Netherlands.
[3] Department of Paediatric Gastroenterology, and Cystic Fibrosis Centre Utrecht, University Medical Centre Utrecht, Utrecht, the Netherlands.

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Abstract

Aim

Pancreatic enzyme replacement therapy (PERT) is the proven therapy to substantially reduce fat malabsorption in cystic fibrosis (CF) patients. Few details of the daily practice regarding PERT and the resulting coefficient of fat absorption (CFA) are known. We therefore recorded the PERT and CFA in a large cohort of pancreatic insufficient paediatric CF patients.

Methods

We retrospectively studied 1,719 completed 3-day dietary food records, including the pancreatic enzyme intake registrations, and 1,373 CFA assessments of 224 CF patients, aged 0 – 17 years. The clinical characteristics, PERT, expressed as an intake of lipase unit (LU)/g fat/day and LU/kg/day, and the CFA were described for the group as a whole, and separately for those on enteral tube feeding. Cross-sectional relationship between the CFA and the LU/g fat/day and LU/kg/day were determined for each year of age. We also addressed the effect of the interventions done in patients with CFA outcomes <85%.

Results

The LU/g fat/day was relatively stable throughout the age groups, while the LU/kg/day fell markedly with age. The median CFA in subsequent age groups varied between 86% and 91%, however, with a CFA <85% in 325 out of the 1,373 measurements (24%). No relationship was found between PERT and CFA. The patients with persistent CFA <85% had significant lower z-scores for weight-for-age and weight-for-height (p 0.01) than those with CFA ≥85%.

Conclusions

In this study population, no correlation between an enzyme dosage and the degree of fat malabsorption was found. However a CFA <85% was found in 24% of the measurements.

Introduction

In most patients with cystic fibrosis (CF), the absence or dysfunction of the cystic fibrosis transmembrane regulator in pancreatic duct cells results in exocrine pancreatic insufficiency,[1] causing an inadequate digestion and leading to fat malabsorption and malnutrition. As a good nutritional status contributes to an improved pulmonary function and survival,[2, 3] a major aim in CF-care is to prevent malabsorption. To this effect, pancreatic enzyme replacement therapy (PERT) is the proven and, therefore, essential therapy, as it will substantially reduce fat malabsorption.[4, 5] The appropriate PERT generally results in a fat absorption in CF patients of more than 85% and, in many patients over 90%.[6] However, very few details of the daily practice on PERT and the coefficient of fat absorption (CFA) in large groups of CF patients are known, as previous studies were rather small and were mainly conducted in the context of a trial.[6] We therefore set out to record the daily practice of PERT and CFA during regular follow-ups of a large cohort of pancreatic insufficient paediatric patients with CF. Subsequently, we analysed PERT and CFA in a subgroup of patients on enteral tube feeding. Finally, we addressed the effect of the interventions done in patients with CFA outcomes <85%.

Methods

Study population

This retrospective study includes Dutch children (born between 1988 and 2012) with proven CF and who received medical care at the CF Centre of the University Medical Centre Utrecht. Each child was confirmed as having CF by a positive sweat test and/or the presence of 2 CF mutations, as well as the clinical signs of CF and/or a positive family history. The pancreatic insufficiency was confirmed as having a documented history of fat malabsorption with a CFA outcome <85%, and/or a faecal elastase concentration <15 µg/g stool or chymotrypsin activity <3 U/g stool. The body-weight and body-height were measured during each routine clinical care visit. Yearly, the dietary data were collected through 3-day dietary food records, which also included a registration of pancreatic enzyme ingestion. Simultaneously, a stool collection was done to measure faecal fat excretion. In all of the patients, the PERT dosage was primarily tailored to their individual dietary fat intake, and subsequent adjusted when the CFA was found to be <85%. Thus, the study's database contained longitudinal data regarding the clinical parameters and the demographics of all of the patients who received medical care for CF at the University Medical Centre Utrecht from 1996 until December 2013. All of the parents provided a written informed consent for the storage and analysis of the data of their

children. The study was performed in accordance with the guidelines of the medical ethics board of the University Medical Centre Utrecht.

Clinical measurements

The body-weight, expressed as kilogram, was measured with a digital weight balance, to the nearest 0.1 kg, and the body-height, expressed as centimetres, was measured with a stadiometer (Holtain, Crymich, UK) to the nearest 0.5 cm. Yearly, all of the CF patients received written instructions on completing a 3-day dietary food record, including a registration of pancreatic enzyme ingestion. The children and parents were encouraged to maintain the child's usual dietary intake. They have been advised to administer an individually worked out single dosage of the pancreatic enzymes before every fat-containing meal, including snacks, fat-containing beverages, and the enteral tube feeding. On each yearly evaluation, the PERT was evaluated and advices were given to match the PERT dosage to the quantity of fat consumed and/or to administer a proton pump inhibitor (PPI).

All of the food and beverages consumed in portion sizes or weights, and the quantity of the pancreatic enzymes actually taken with each meal, were recorded during 2 weekdays and 1 weekend-day whenever possible. Where weights were not specified, the portion size weights were obtained from the reference data. The enteral tube feeding was recorded as type and volume within the diaries. Registered dieticians coded and analysed the food records according to a standardised approach, using the Dutch Food Composition Table (2010) of the Dutch Nutrition Centre.[7] The mean daily dietary fat intake was calculated for each assessment and expressed as both gram and energy percentage (En%) of the total energy intake. The recorded pancreatic enzyme ingestion varied in the amount of lipase unit (LU)/dosage and reported as the total LU intake/day, LU/g fat/day, and LU/kg/day.

A fat balance study was performed to measure the fat excretion in faeces, analysed by near infrared spectroscopy, and to calculate the CFA. To this effect, in conjunction with the 3-day dietary food record, a home-based 72-hour stool collection was obtained, starting on day 2 and ending on day 4, to determine the mean faecal fat content of this 3-day collection. The CFA was then calculated from the mean dietary fat intake of the 3-day dietary record and the mean pooled faecal fat output and expressed as a percentage.

Statistics

The descriptive statistics of the categorical variables of the study sample were examined. Due to the repeated measurements of individual patients at different years of age, the children were stratified according to age year (0 year = birth to <1 year, 1 year = 1 to <2 years, etc.). We described the mean (± standard deviation) of body-weight, dietary fat intake, and the median (25^{th} – 75^{th} percentiles) of LU/day, LU/g fat/day, LU/kg/day, and CFA for the total group and apart for those who have enteral tube feeding. We then determined the cross-sectional relation between LU/g fat/day, LU/kg/day, and CFA for the total group and apart for those with a CFA outcome <85% by using the Spearman's correlation coefficient. We also compared the CFA between those with and without enteral tube feeding by using the Mann-Whitney test. Subsequently, we compared the intake of LU/g fat/day, and LU/kg/day among the categorised groups of CFA by using the Kruskal-Wallis test. For this purpose, the children were subdivided based on their CFA as having an outcome <85%, between 85% and 90%, between 90% and 95%, and >95%. Additionally, the effect of the interventions done in patients with CFA outcomes <85% was addressed. For this purpose, the patients with at least 2-consecutive yearly measurements, with initial CFA outcomes <85%, were included. We described the intervention given and compared the age, PERT, nutritional status expressed as z-scores for weight-for-age, height-for-age, and weight-for-height, the use of PPI and ursodeoxycholic acid (UDCA) among the patients with CFA outcomes <85% and ≥85% after an intervention done by using the *t*-test, Mann-Whitney test or chi-squared test. The statistical analyses were performed using the Statistical Package for the Social Sciences Computer Software (SPSS Inc., version 20, IBM, Chicago, IL). All of the values were considered significant at $p<0.05$.

Results

Clinical characteristics

The data of 224 patients (98% Caucasian, 48% girls) with CF were analysed. All were confirmed to be pancreatic insufficient and had PERT. A total of 1,719 completed 3-day dietary food records, including the pancreatic enzyme intake registrations, and 1,373 completed CFA assessments were obtained. The study enrolled 32 patients (accounted for 234 food records/194 CFA measurements) diagnosed by a meconium ileus, 44 patients (148 records/104 CFA) who were provided enteral tube feeding, 107 patients (665 records/554 CFA) who had prescribed PPI, 67 patients (375 records/67 CFA) who had prescribed UDCA of which 3 patients (11 dietary food records/9 CFA) were known to have liver cirrhosis.

Dietary fat intake and PERT

The included patients were stratified according to the age year. Patients obtained between 34% and 36 En% of the total energy intake from fat. With the exception of infants, PERT, expressed as median LU/g fat/day, seems relatively stable. When PERT was expressed as LU/kg/day, the children up to 9 years of age had overall intakes >5,000 LU/kg/day, and thereafter the supplementation fell markedly with age (Figure 1, see also Supplemental Table 1 for detailed information). A PERT intake >10,000 LU/kg/day was found in 26 measurements (16 patients).

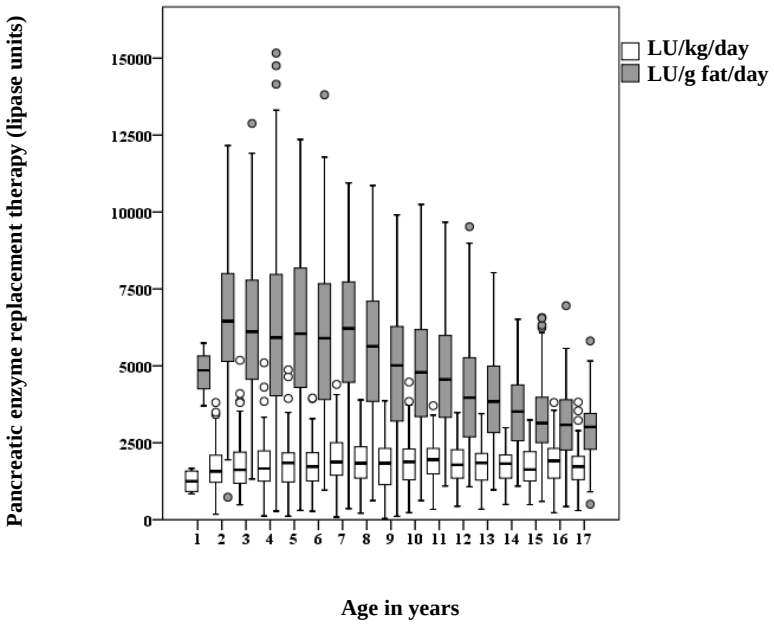

Figure 1. Pancreatic enzyme replacement therapy, expressed as lipase units/kg body-weight/day (LU/kg/day) and lipase units/gram dietary fat intake/day (LU/g fat/day) set out against age in years, derived from 1,719 measurements of 224 patients with cystic fibrosis.

CFA

The CFA varied between 86 and 91% with a large range in the outcomes in the different age groups (Figure 2, see also Supplemental Table 1 for detailed information). For patients who had both a PERT and a CFA measurement, we found no relation between either LU/g fat/day and CFA, or, LU/kg/day and CFA, apart from age group 17 (r_s=0.526 p=0.04). Also in 325 records (24%), in which the CFA was <85%, we found no correlation between the PERT and CFA. Subsequently, the PERT was analysed in 4 categories: CFA <85%, between 85% and 90%, between 90% and 95% and >95% in which we found the same distribution of PERT (p≥0.055).

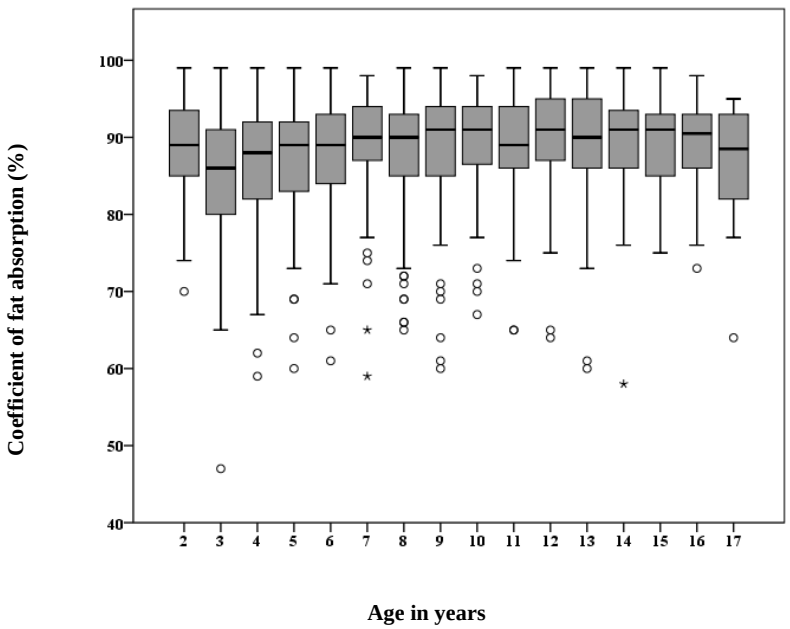

Figure 2. Coefficient of fat absorption (%), set out against age in years, derived from 1,373 measurements of 203 patients with cystic fibrosis.

PERT and CFA in patients on enteral tube feeding

All patients receiving (nocturnal) enteral tube feeding used a non-elemental formula, which provided 9% up to 99% of the total energy intake. The patients on enteral tube feeding had more or less similar PERT; intakes varying over the age groups between 1,359 and 2,043 LU/g fat/day, and 3,959 and 7,627 LU/kg/day. The CFA varied between 91% and 96% and was higher in the children with the enteral tube feeding and significantly so in age groups 3, 5, 6, 7, 9, and 12 (p≤0.024) (Figure 3).

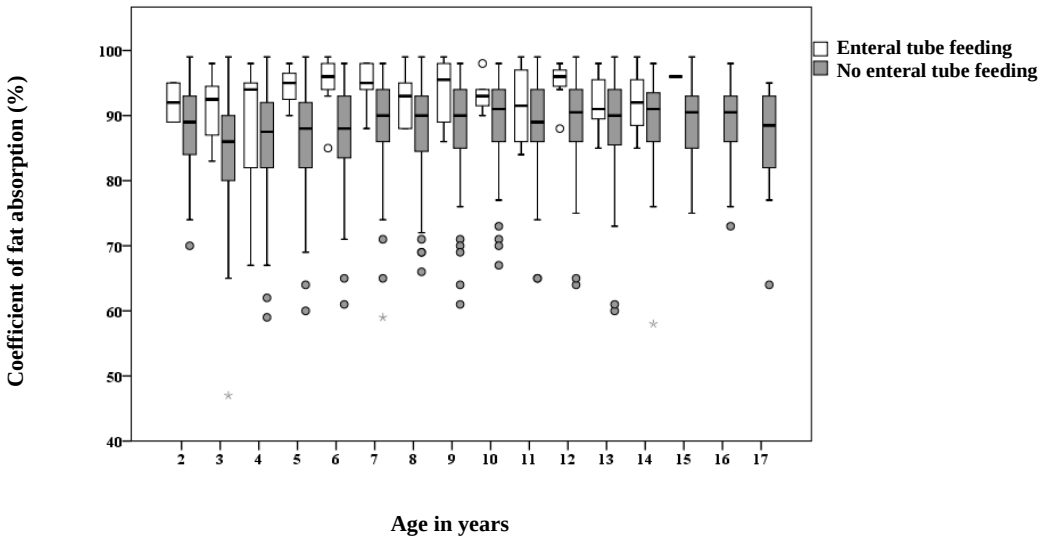

Figure 3. Coefficient of fat absorption (%), subdivided into outcomes of those who were provided enteral tube feeding and those without enteral tube feeding, set out against age in years, derived from 1,373 measurements of 203 patients with cystic fibrosis (39 patients on enteral tube feeding, accounted for 104 measurements).

Interventions done in the patients with consecutive yearly CFA measurements with a CFA <85% in the first measurement

In 170 measurements at least two 2-consecutive yearly measurements, with a CFA <85% in the first measurement, were available, enabling us to study the effect of interventions done. After the first intervention, in which PERT and/or PPI dosage was adjusted in almost all patients (Table 1a), the CFA remained <85% in 57 measurements. Subsequently, follow-up data of a second intervention was available for 47 out of the 57 measurements. In these patients, the CFA remained <85% in 19 measurements (Table 1b). Follow-up data of a third intervention was available for 18 out of the 19 measurements (Table 1a). Despite an increase in PERT and/or PPI, the CFA remained <85% in 11 measurements. We found no differences in age, or in the use of PERT, PPI and UDCA between patients with a CFA ≥85% and those with a CFA <85%. However, patients with a CFA <85% during 3-consecutive yearly measurements had significantly lower z-scores for weight-for-age and for weight-for-height (p 0.01) than those with a CFA ≥85% after the third intervention (Table 1b).

Table 1a. Interventions given in patients who had consecutive-yearly CFA measurements with a CFA <85%

Intervention	1st intervention	2nd intervention	3rd intervention
	N	N	N
Increase PERT	74	15	6
Start PPI	35	11	-
Increase PERT + start PPI	48	14	11
Other (e.g. PERT / PPI unaltered)	13	7	1

N = number of measurements PERT = pancreatic enzyme replacement therapy
PPI = proton pump inhibitor

Discussion

The current study, including 224 patients who completed 1,719 3-day dietary food records and 1,373 CFA measurements, is the largest study currently available describing the daily use of PERT and the resulting CFA as measured in a 72-hour stool collection in a cohort of CF patients. With the CFA outcomes between 86% and 91% throughout the age groups, although with large ranges in outcomes, our results are in concordance with previous results.[6, 8, 9] An enormous variability in the response to PERT among patients was found,[10-12] with no clear correlation between the CFA and PERT, as previously reported.[11-13] The PERT dosage, expressed as LU/g fat/day, was fairly constant, but gradual became lower when expressed as LU/kg/day, as a consequence of the lower caloric and fat intake per kilogram body-weight with increasing age. The current international guidelines aim to keep PERT <10,000 LU/kg/day[4, 5] to avoid fibrosing colonopathy.[14] This study found in less than 2% of the measurements an intake in excess of this limit. It is unlikely that increasing PERT beyond the threshold of 10,000 LU/kg/day[4, 5] will produce any benefit with respect to either fat malabsorption[15, 16] or growth.[17] This is supported by a study in which children who initially received more than 11,000 LU/kg/day reduced their PERT dosage to less than 10,000 LU/kg/day, but still had CFA outcomes ≥92%, while growth parameters even improved.[18] The suggestion that the use of high strength enzyme preparations carries a greater risk of exceeding this upper limit [19] is not supported by our results, as high strength preparations were used in 7% (121 out of 1,719 measurements), with only 1 patient exceeding the 10,000 LU/kg/day threshold.

Table 1b. Clinical characteristics of patients who had consecutive-yearly CFA measurements after a CFA <85% was found. CFA outcomes after each subsequent measurement were categorized as having a CFA< or ≥85%. Included were respectively 170 measurements of 118 patients after a first intervention, 47 measurements of 45 patients after a second intervention and 18 measurements of 18 patients after a third intervention.

	CFA after 1st intervention			**CFA after 2nd intervention**			**CFA after 3rd intervention**		
	<85% (n = 57)	**≥85% (n = 113)**	***p***	**<85% (n = 19)**	**≥85% (n = 28)**	***p***	**<85% (n = 11)**	**≥85% (n = 7)**	***p***
Age	7.96 ± 3.5	8.82 ± 3.78	0.15	8.26 ± 3.44	8.40 ± 2.66	0.88	8.46 ± 2.93	9.47 ± 3.11	0.50
CFA	77 ± 7	90 ± 3	0.00	76 ± 8	92 ± 3	0.00	74 ± 9	92 ± 5	0.00
LU/g/fat	2,090 (1,403 – 2,589)	1,882 (1,443 – 2,344)	0.44	1,496 (1,244 – 2,427)	2,000 (1,469 – 2,449)	0.33	2,296 (1,473 – 3,448)	1,988 (1,016 – 2,070)	0.21
LU/kg	5,375 (3,222 – 7,629)	5,053 (3,748 – 6,574)	0.64	3,494 (2,500 – 6,328)	5,962 (3,887 – 7,516)	0.03	7,368 (5,637 – 8,676)	6,198 (2,752 – 6,842)	0.29
WFA	-0.33 ± 1.05	-0.17 ± 0.94	0.29	-0.36 ± 1.19	-0.43 ± 0.85	0.82	-0.79 ± 0.74	0.48 ± 1.23	0.01
HFA	-0.61 ± 1.00	-0.37 ± 1.08	0.18	-0.69 ± 0.99	-0.75 ± 0.86	0.82	-0.87 ± 0.79	-0.31 ± 1.11	0.23
WFH	-0.04 ± 0.94	-0.06 ± 0.82	0.92	-0.02 ± 0.95	-0.09 ± 0.84	0.79	-0.42 ± 0.76	0.73 ± 0.85	0.01
PPI (n)	28	55	0.96	6	14	0.51	6	3	nd
UDCA (n)	16	27	0.55	7	5	nd	5	2	nd

CFA = coefficient of fat absorption
HFA = z-score height-for-age
WFH = z-score weight-for-height
LU = lipase units
WFA = z-score weight-for-age
PPI = proton pump inhibitor
nd = not defined
UDCA = ursodeoxycholic acid

The patients with (nocturnal) non-elemental enteral tube feeding were advised to ingest PERT in a single dosage at the beginning of the tube feeding. Nevertheless, despite the often long infusion period, these patients had better CFA outcomes than the group without the tube feeding, which could be related to the liquid emulsion form of enteral tube feeding, which may provide a more optimal substrate for pancreatic enzyme activity. This study supports the common advice of a single dosage of enzymes before the beginning of the (nocturnal) non-elemental enteral tube feeding.

It is believed that with close monitoring, PERT should be able to improve the CFA to more than 85%.[5] However, in this study, it failed in 24% of the CFA measurements, although PERT was similar in both the group with a CFA <85% and a CFA ≥85%. A substandard individual response to PERT, resulting in a CFA <85%, can be due to a lack of adherence to the treatment.[20] Other possible causes are small bowel bacterial overgrowth due to the antibiotic treatment, which is seen in a substantial proportion of CF patients,[21] and mucosal disorders, including celiac disease.[22] Constipation, which is often seen in patients with CF, is associated with lower CFA outcomes.[23] Likely, in certain situations, a laxative treatment might improve the CFA, as it normalises the intestinal transit time; in addition, it may improve the bacterial overgrowth.[24, 25] The individual variation in the faecal bile salt loss, which is seen in CF,[26] may lead to a reduced solubilisation capacity of bile, resulting in fat malabsorption. However, this suggestion is not supported by the study results describing that the faecal bile salt malabsorption does not contribute to the fat malabsorption.[26, 27] Furthermore, it could be hypothesised that patients on UDCA treatment have a decreased fat absorption, as UDCA is less hydrophobic and has an impaired capability in forming mixed micelles.[28] Nevertheless, the results of the relatively small studies did not find an association between the UDCA treatment and the CFA;[29, 30] nor did our study. The low intraluminal pH will compromise the pancreatic lipase activity due to a delay in the dissolution of the acid-resistant enteric coating.[31] Increasing the gastric pH to a level that is favourable for the optimal release of enzymes by the concomitant use of PPI may protect the inactivation of the enzymes and improve efficacy.[4] However, a significant positive effect of the gastric acid suppressant therapy on CFA is not fully demonstrated[9, 32, 33] as was also found in this study; patients on PPI still had recurrent CFA <85%. The PPI possibly only improves the efficacy of PERT in patients with a low duodenal pH and will not affect the CFA outcomes in those with an optimum pH for enzyme release already.

The calculation of the CFA is based on the assessment of the difference between the average 3-day dietary fat intake and the average daily faecal fat output of the 72-hour stool collection. Therefore, the accuracy of the CFA outcome may be influenced by over- and/or under-reporting of the dietary (fat) intake, or by the failure to collect the stool for the entire period, whereby the excreted fat will not be completely measured. In addition, we could not objectively measure the adherence to PERT or the timing of PERT ingestion in relation to the meals, which is another limitation of this study.

Conclusions

PERT in patients with CF is assumed to result in a CFA above 85%; nevertheless, in this study, this threshold was not passed in over 20% of the measurements. Furthermore, no correlation between the enzyme dosage and the degree of fat malabsorption was found, which might be the result of the factors residing in the gastrointestinal tract (e.g. persistent low intraluminal pH, slow transit, and abnormal bile acid metabolism) or outside the gastrointestinal tract (i.e. insufficient compliance).

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Supplemental Table 1. Dietary fat intake, coefficient of fat absorption, and pancreatic enzyme replacement therapy derived from 1,719 completed 3-day dietary food records of 224 patients (108 girls) with cystic fibrosis.

Age	N	Weight kg	Fat g	Fat En%	% CFA (median) (25^{th} – 75^{th} percentiles)	LU/day	LU/g fat/day	LU/kg/day
1	4	11.1 ± 1.3	45 ± 11	34 ± 5	-	53,875 ± 14,890	1,252 ± 395	4,789 ± 837
2	93	13.3 ± 1.8	54 ± 16	35 ± 6	89 (84 – 94) (n = 59)	88,688 ± 40,063	1,754 ± 862	6,698 ± 2,975
3	115	15.7 ± 2.3	57 ± 14	34 ± 5	86 (80 – 91) (n = 93)	95,929 ± 40,742	1,748 ± 811	6,195 ± 2,671
4	116	17.5 ± 2.3	61 ± 16	34 ± 6	88 (82 - 92) (n = 96)	105,409 ± 50,121	1,772 ± 843	6,118 ± 2,841
5	133	19.8 ± 2.9	68 ± 15	35 ± 6	89 (83 – 92) (n =111)	117,805 ± 48,587	1,777 ± 813	6,030 ± 2,520
6	124	22.2 ± 3.1	75 ± 18	36 ± 5	89 (84 – 93) (n = 110)	128,738 ± 49,346	1,769 ± 684	5,917 ± 2,418
7	121	25.0 ± 3.8	78 ± 20	36 ± 6	90 (87 – 94) (n = 105)	146,840 ± 54,647	1,959 ± 812	5,965 ± 2,273
8	135	27.5 ± 3.2	83 ± 19	36 ± 5	90 (85 – 93) (n = 122)	149,753 ± 56,070	1,845 ± 709	5,517 ± 2,087
9	142	30.8 ± 4.0	88 ± 23	36 ± 6	91 (85 – 94) (n = 124)	149,225 ± 61,456	1,779 ± 767	4,874 ± 2,019
10	133	33.5 ± 5.1	90 ± 21	36 ± 5	91 (86 – 94) (n = 115)	158,433 ± 64,290	1,819 ± 753	4,851 ± 2,025
11	133	37.3 ± 5.5	94 ± 24	36 ± 5	89 (86 – 94) (n = 103)	169,716 ± 65,650	1,851 ± 697	4,652 ± 1,951
12	111	42.2 ± 7.0	94 ± 25	35 ± 5	91 (87 – 95) (n = 81)	167,668 ± 65,405	1,830 ± 689	4,123 ± 1,831
13	110	46.4 ± 6.9	105 ± 26	36 ± 5	90 (86 – 95) (n = 90)	176,816 ± 66,902	1,742 ± 654	3,879 ± 1,567
14	88	51.3 ± 7.7	106 ± 29	35 ± 5	91 (86 – 94) (n = 63)	178,073 ± 65,535	1,738 ± 582	3,537 ± 1,364
15	71	56.1 ± 8.2	106 ± 27	35 ± 5	91 (85 – 93) (n = 47)	179,949 ± 65,132	1,763 ± 682	3,275 ± 1,300
16	53	58.5 ± 8.1	106 ± 35	34 ± 5	91 (86 – 93) (n = 38)	186,836 ± 71,921	1,870 ± 730	3,203 ± 1,250
17	37	62.9 ± 7.9	114 ± 47	35 ± 5	89 (82 – 93) (n = 16)	189,995 ± 72,635	1,813 ± 752	3,018 ± 1,116

En% = percentage of energy CFA = coefficient of fat absorption LU = lipase units

Part 2

Body-growth in children and adolescents with cystic fibrosis

5

The relationship between body-growth and pulmonary function in children with cystic fibrosis

J.W. Woestenenk [1]
R.K. Stellato [2]
S.W. Terheggen-Lagro [3]
C.K. van der Ent [3]
R.H.J. Houwen [4]

[1] Internal Medicine and Dermatology, Dietetics and, Cystic Fibrosis Centre Utrecht, University Medical Centre Utrecht, Utrecht, the Netherlands.
[2] Department of Biostatistics, Julius Centre, University Medical Centre Utrecht, Utrecht, the Netherlands.
[3] Department of Paediatric Pulmonology, and Cystic Fibrosis Centre Utrecht, University Medical Centre Utrecht, Utrecht, the Netherlands.
[4] Department of Paediatric Gastroenterology, and Cystic Fibrosis Centre Utrecht, University Medical Centre Utrecht, Utrecht, the Netherlands.

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Abstract

Aim

To measure the weight and height of children with cystic fibrosis (CF) from 2 to 10 years of age and to investigate the relationship between these parameters and forced expiratory volume in 1 second (FEV_1) beginning at 6 years of age.

Methods

Weight and height were expressed as z-scores for weight-for-age (WFA), height-for-age (HFA), height-adjusted-for-target-height (HFA/TH) and weight-for-height (WFH). The children were categorised as having a z-score ≥0, between 0 and -1, or <-1 based on z-scores at age 2. The cross-sectional and longitudinal relationships between FEV_1 and WFA, HFA, HFA/TH, and WFH were determined and the predictive value of these parameters for FEV_1.

Results

We enrolled 156 children with CF. Their mean weight and height were below the average for the healthy population. Both WFA and WFH increased with age, primarily before the age of 6, while the reduction in HFA and HFA/TH persisted. Importantly, the yearly decline in FEV_1 was significantly slowed by 1.8 and 1.9% for each unit increase in WFA and WFH ($p<0.015$) in children who gained weight.

Conclusion

CF patients aged 2 to 10 years have long-term impaired growth. Nevertheless, weight gain slowed the decline in FEV_1 in these patients.

Introduction

Cystic fibrosis (CF) is a life-threatening genetic disorder characterised by chronic pulmonary inflammation that causes a gradual, progressive decline in pulmonary function (PF). Most CF patients also have pancreatic insufficiency, leading to intestinal malabsorption. Thus, both chronic pulmonary inflammation and the intestinal malabsorption are associated with poor nutritional status.

Lung disease and nutritional status are closely related[1] such that weight can affect PF and vice-versa.[2] Moreover, several studies have shown that weight gain leads to an improved PF,[3-5] whereas weight loss can accelerate the decline in PF.[5] Weight and height also have prognostic value for predicting PF.[6,7] For example, children with low body-weight at 3 years of age have reduced forced expiratory volume in 1 second (FEV_1) at 6 years of age,[3] and children who are in the bottom 5^{th} percentile for height at 5 – 7 years have a higher mortality rate than taller children.[8] However, in order to assess nutritional status, height can only be fully appreciated when it is corrected for genetic components, for example by correcting for target height (TH).[9] Although lung disease and nutritional status are associated, the long-term relationship between FEV_1 and factors such as weight, height, and height-adjusted-for-TH are poorly understood, as most studies included a follow-up period of ≤ 3 years only.[3] To address these relationships over a much longer period of time, we retrospectively studied weight, height and height-adjusted-for-TH from 2 through 10 years. In addition, we investigated the relationship between these parameters and FEV_1 in children with CF at age 6 years and older.

Materials and methods

Study population

This retrospective study included Dutch children (born between 1988 and 2011) with proven CF and who received medical care at the CF-centre of the University Medical Centre Utrecht. Each child was confirmed as having CF by a positive sweat test and/or the presence of 2 CF-mutations, as well as clinical signs of CF and/or a positive family history. Weight, height and beginning at age 4 years, pulmonary function (PF) were measured during each routine clinical care visit. Thus, the study's database contained longitudinal data regarding the clinical parameters and demographics of all children who received medical care for CF at the University Medical Centre Utrecht from 1988 through December 2011. This study included children, aged 2 to 10 years, who were receiving pancreatic enzyme replacement therapy, whose weight and/or height were measured at 2 years of age, and whose weight, height, and

PF were measured at least twice at age 6 years and older. All patients (or the parents of young patients) provided written informed consent for the storage and analysis of their data. The study was performed in accordance with the guidelines of the medical ethics board of the University Medical Centre Utrecht.

Clinical measurements

Pulmonary function, assessed by FEV_1, was obtained from maximal expiratory flow curves (Masterscreen, Viasys Healthcare, Höchberg, Germany) and is expressed as the percentage of the predicted value for a given height and gender (FEV_1% pred.).[10] For each child, the highest FEV_1% pred. measured in the preceding calendar year (beginning at 6 years of age) was used in the analysis. The patients were subdivided into 5 classes based on their CF-transmembrane-conductance-regulator-mutation. Patients who were either homozygous or compound heterozygous for a class I, class II or class III mutation were then classified as severe, and patients who carried at least 1 class IV or class V mutation were classified as mild.[11] Children with missing data regarding their mutation were classified as unknown.

Weight and height measurements

Weight was measured to the nearest 0.1 kg using a digital scale, and height was measured to the nearest 0.5 cm using a stadiometer (Holtain, Crymich, UK). Both weight and height were compared to reference values for Dutch children by converting the values to z-scores for weight-for-age (WFA), height-for-age (HFA), and weight-for-height (WFH) using specialised software (Growth Analyser 4 RCT, 2010, Dutch Growth Foundation). TH was calculated using the height of the patient's biological parents. Formulas for calculating the TH and the z-score for TH were based on a nationwide growth study in the Netherlands.[12] These formulas adjust for genetic potential in children with discordant parents.[13] The z-score for height-adjusted-for-target-height (HFA/TH) was calculated by subtracting TH from HFA.[14]

Statistics

Descriptive statistics of FEV_1% pred. and WFA, HFA, HFA/TH, and WFH were calculated. The variables were tested for normality and skewness, and the correlations between FEV_1% pred. and WFA, HFA, HFA/TH, and WFH were measured at age 6 to 10 (with a 2-year interval between measurements). The children were then categorised as having a z-score ≥ 0, a z-score between 0 and -1, or a z-score <-1 based on their initial z-scores (at age 2). We then examined WFA, HFA, HFA/TH, WFH, and FEV_1% pred. for the categorised z-scores at age 2

and in subsequent 2-year intervals. For the longitudinal analyses, one-way analysis of variance (ANOVA) with the Tukey's test was used to assess the association between the categories of z-scores at age 2 and FEV_1% pred. at age 6 to 10 years. In addition, linear mixed-model regression was used to evaluate the effects of weight and height in the categorised WFA, HFA, HFA/TH, and WFH at age 2 on longitudinal changes in FEV_1% pred.; because of multicollinearity, separate models were developed for weight and height. This model allows inclusion of variable numbers of measurements per child and irregularly timed and missing observations. The following confounders were included in the model: gender, cohort effect (grouped as children who were born before 1996, from 1996 through 2001, or after 2001), age at diagnosis (grouped as diagnosed before or after 1 year of age), CF-genotype (grouped as severe, mild, or unknown), and meconium ileus (grouped as present or absent). A random intercept and random effect for age per child was included in the models to account for differences between children. The likelihood ratio test was used to determine the effect of excluding a variable from the model, and $p<0.05$ was used as the threshold for statistical significance. Statistical analyses were performed using the Statistical Package for the Social Sciences program (SPSS, version 20, IBM, Chicago, IL).

Results

A total of 156 children with proven CF (96% Caucasian) with a mean follow-up period of 7.4 ± 1.0 years were eligible for inclusion (see Table 1 for baseline characteristics). None of these children were diagnosed using newborn screening, as this method was introduced in May 2011. Twenty-three children (15%) did not receive sufficient calories for adequate growth and were started on enteral tube feeding during the follow-up period; 16 (70%), 11 (48%), 9 (39%), and 12 (52%) of these 23 children had respective initial WFA, HFA, HFA/TH, and WFH z-scores of <-1. At the time of inclusion (ie. at age 2), approximately 75% of the patients had a z-score <-1 (Table 1).

We found no association between any z-score category and meconium ileus, age at diagnosis, ethnicity, genotype, gender, or year of birth. In the 8 years following enrolment in the study (i.e. from age 2 until 10 years), the z-scores for WFA and WFH increased by approximately 0.4, whereas HFA and HFA/TH were unchanged (Figure 1). Moreover, FEV_1% decreased by 2.2% each year from 6 until 10 years. We found no significant cross-sectional correlation between FEV_1% and either weight or height.

Table 1. Baseline characteristics of 156 children with cystic fibrosis.

		N (%)
Age at inclusion		2.3 ± 0.2 y
Girls		72 (46)
Born	before 1996	53 (34)
	between 1996 and 2001	66 (42)
	after 2001	37 (24)
Diagnosed in 1st year of life		121 (78)
Meconium ileus		27 (17)
Genotype	Severe	141 (90)
	Mild	4 (3)
	Unknown	11 (7)
Weight-for-age at inclusion (z-score)		-0.65 ± 1.04
	≥0	40 (26)
	<0 and ≥-1	58 (37)
	<-1	58 (37)
Height-for-age at inclusion (z-score)		-0.61 ± 1.00
	≥0	37 (24)
	<0 and ≥-1	67 (43)
	<-1	52 (33)
Height-adjusted-for-target-height at inclusion (z-score) (n = 151)		-0.45 ± 0.94
	≥0	43 (28)
	<0 and ≥-1	69 (46)
	<-1	39 (26)
Weight-for-height at inclusion (z-score)		-0.33 ± 1.1
	≥0	36 (23)
	<0 and ≥-1	67 (43)
	<-1	53 (34)

For further analyses, the children were categorised based on their WFA, HFA, HFA/TH and WFH at age 2 into z-score ≥0, z-score between 0 and -1, or z-score <-1 categories. The development of each parameter for nutritional status, as well as FEV_1% pred., was followed at 2-year intervals for the categorised z-scores beginning at 2 years of age (Figure 2). The cross-sectional averages of categorised WFA and WFH revealed a regression to the mean,

particularly before age 6. Children who had both WFA and WFH ≥0 at age 2 had a slight decline, whereas children whose initial WFA and WFH were <0 improved during the follow-up period. Children whose HFA was ≥0 or <-1 also showed a regression to the mean, particularly below the age of 6; in contrast, children who started with HFA between 0 and -1 had relatively stable growth. Similar results were obtained with respect to HFA/TH. It is important to note that despite this regression to the mean, the children who had a negative z-score at 2 years of age had lower z-scores at 10 years of age compared to children whose initial z-score was ≥0; this was particularly true for HFA and HFA/TH.

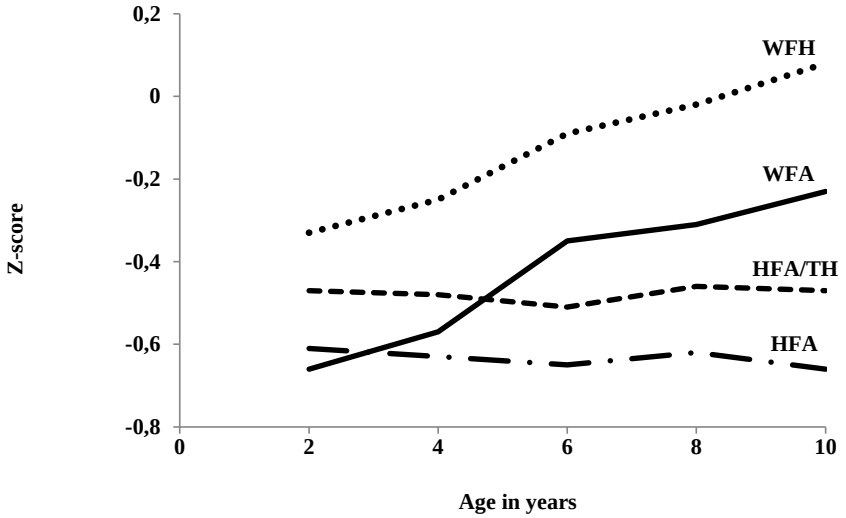

Figure 1. Mean z-scores for weight-for-age (WFA), height-for-age (HFA), height-adjusted-for-target-height (HFA/TH) and weight-for-height (WFH) plotted against age in years in 156 children with cystic fibrosis.

With respect to PF, children with an initial z-score ≥0 had higher FEV_1% pred. at age 6 than children whose initial z-score was <0. However, the patients whose initial z-score was ≥0 had a faster decline in FEV_1% pred. than children whose initial z-score was <0. This resulted in nearly similar FEV_1% pred. values at the age of 10 for all categories, with the exception of children whose initial z-score for WFA or WFH was <-1. This difference in FEV_1% pred. was significant (p=0.047 and p=0.019 for WFA and WFH) at 6 years of age and significant for WFH (p=0.005), but not WFA, at 10 years of age.

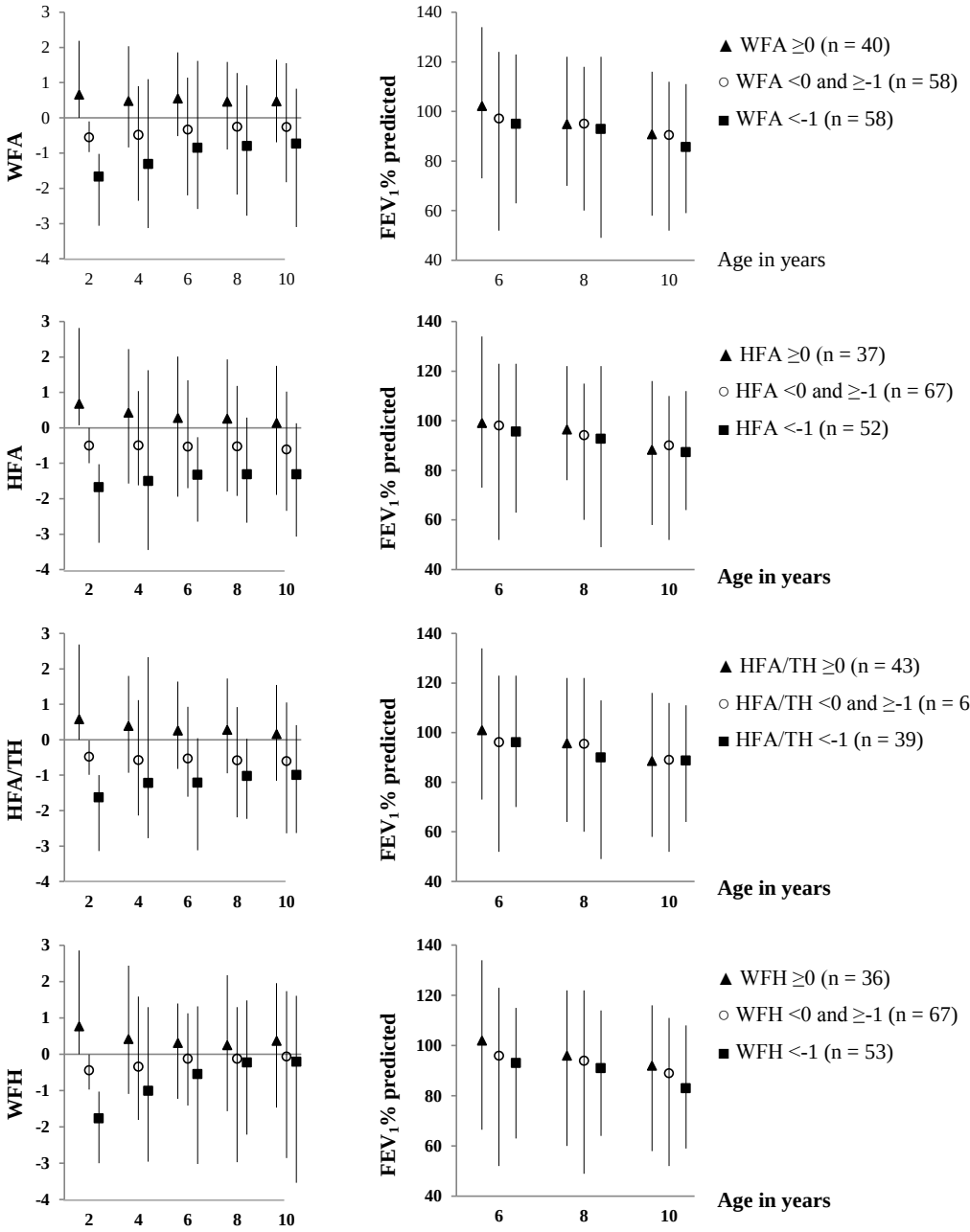

Figure 2. Z-scores for weight-for-age (WFA), height-for-age (HFA), height-adjusted-for-target-height (HFA/TH) and weight-for-height (WFH), expressed as mean (symbol) with confidence interval (vertical line), and forced expiratory volume in 1 second % predicted (FEV_1% pred.) for the categorised z-scores at 2 years of age in 156 children with cystic fibrosis.

Our mixed-model revealed that on average, children with an initial z-score ≥0 had a higher estimated FEV_1% pred. at age 6 compared with children whose initial z-scores were <0; nevertheless, all groups had relatively large confidence intervals, indicating high variability among individuals. The annual decline in FEV_1% pred. also varied widely between individuals throughout the study, and this decline was not dependent on the child's initial weight or height. Importantly, regardless of their initial WFA or WFH category, the children who increased in weight had significant smaller declines in FEV_1% pred. from age 6 to 10 years; the decline in FEV_1% slowed by 1.8% and 1.9% for each unit increase in WFA and WFH, respectively (Table 2). This effect was not observed with respect to either HFA or HFA/TH (Supplemental Table 1).

Discussion

Here, we report that both weight and height are below average for children with CF at age 2. However, children with below-average WFA and WFH caught up during the subsequent 8 years, whereas HFA and HFA/TH were unchanged. Although this increased growth with respect to WFA and WFH may be explained by regression to the mean, it may also be due to nutritional support, which is an integral part of the multidisciplinary care of patients with CF, [15, 16] as children with lower z-scores may have received more aggressive nutritional care. Similarly, well-nourished children and/or children whose z-scores were consistently >-1 could have been judged as doing relatively well and therefore received less aggressive nutritional care.

We found that, although the weight and height of these children were below average at age 2, they did not reach levels comparable to children whose initial z-scores were ≥0. This was particularly true for children with below-average HFA and/or HFA/TH, suggesting that impaired height at age 2 can be long-term and is likely permanent. Therefore, the first 2 years of life are extremely important for adequate growth, consistent with reports that children who are diagnosed using newborn screening have significantly higher WFA and HFA than children who were not diagnosed using newborn screening.[17, 18] Children who were not diagnosed as newborns had a much larger decline in WFA and HFA during the first 6 months of life; moreover, although these children improved after diagnosis, their delay in HFA was long-term (lasting until 7.5 to 12 years)[19, 20] or even permanent.[18]

A prospective observational study of 3,142 CF patients using data obtained from the Cystic Fibrosis Foundation Registry in the United States[7] found that children with low WFA at 4

years had lower FEV_1% pred. values in successive years, although the rate of decline in FEV_1% pred. was similar for all WFA categories. Consistent with these results and others,[3] we found that children with initial WFA or WFH <-1 (ie. at 2 years) had lower FEV_1% pred. values at 6 years. We also found that children who were able to gain weight slowed their decline in FEV_1% pred. by nearly 2 percentage points for each unit increase in either WFA or WFH. This finding is consistent with previous studies.[3,4]

It is important to note that we did not find any association between FEV_1 and either HFA or HFA/TH, even though other studies have reported that the rate of increase in height was associated with lung disease.[6, 7] However, in these previous studies, the impaired growth with respect to height was particularly apparent during puberty,[6, 7] during which the largest increase in height occurs and is linearly correlated with increasing lung volume.[21] Because we studied children up to the age of 10 years, the influence of growth spurts during puberty could not be assessed. Furthermore, the direction and magnitude of the rate of decline in FEV_1% pred. did not depend significantly on initial WFA, HFA, or HFA/TH. Nevertheless, FEV_1% pred. decreased more rapidly in children with higher FEV_1% pred. at 6 years, which is consistent with previous results.[2]

Because this study included patients who were treated at a single centre, the results cannot be widely generalised to other CF-treatment centres and populations. Moreover, the relatively small sample size may have limited our power to observe some differences. Finally, this was a retrospective study, and data regarding corticosteroid use and chronic inflammation were not included in the analyses; therefore, the reported associations do not necessarily reflect causality.

Conclusions

Impaired growth in CF patients 2 to 10 years of age is long term and can be permanent, particularly with respect to height. Regardless of the patient's WFA and WFH at 2 years, gaining weight during growth can slow the decline in pulmonary function. These results underscore the importance of diagnosing CF early and initiating nutritional intervention as early as possible. Our results also highlight the need for longitudinal screening of both weight and height in all children with CF in order to prevent impaired growth and minimise the decline in pulmonary function.

Table 2. Effect of initial z-scores for weight-for-age and weight-for-height at age 2 years on longitudinal changes in forced expiratory volume in 1 second in 156 children with cystic fibrosis*.

Model WFA	***Intercept* FEV$_1$% pred. age 6**	**Standard Error *b***	**95% Confidence interval**
WFA ≥0	100.4	2.2	96.1 – 104.8
WFA <0 and ≥-1	99.8	2.9	89.8 – 109.8
WFA <-1	97.8	3.0	87.7 – 108.1
	***b* FEV$_1$% pred. / year**		
WFA ≥0 * age	-2.6	0.5	-3.6 – -1.5
WFA <0 and ≥-1 * age	-2.2	0.7	-4.6 – 0.2
WFA <-1 * age	-2.2	0.7	-4.6 – 0.1
Increase of 1 z-score WFA	1.8	0.7	0.3 – 3.2
Model WFH	***Intercept* FEV$_1$% pred. age 6**	**Standard Error *b***	**95% Confidence interval**
WFH ≥0	100.9	1.9	97.2 – 104.6
WFH <0 and ≥-1	99.3	2.9	90.6 – 107.9
WFH <-1	95.2	2.5	85.8 – 104.7
	***b* FEV$_1$% pred. / year**		
WFH ≥0 * age	-2.4	0.4	-3-3 – -1.5
WFH <0 and ≥-1 * age	-2.2	0.6	-4.3 – -0.2
WFH <-1 * age	-2.5	0.7	-4.7 – -0.8
Increase of 1 z-score WFH	1.9	0.6	0.8 – 3.1

FEV$_1$% pred. = forced expiratory volume in 1 second % predicted

WFA = z-score weight-for-age WFH = weight-for-height

* Corrected for gender, birth cohort, age of diagnose, CF-genotype, meconium ileus

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Supplemental Table 1. Effect of initial z-scores for height-for-age and height-adjusted- for-target-height at age 2 years on longitudinal changes in forced expiratory volume in 1 second in 156 children with cystic fibrosis*.

Model HFA	***Intercept* FEV_1% pred. age 6**	**Standard Error *b***	**95% Confidence interval**
HFA ≥0	100.7	2.2	96.3 – 105.1
HFA <0 and ≥-1	99.4	2.8	89.6 – 109.3
HFA <-1	96.1	2.9	85.9 – 106.1
	***b* FEV_1% pred. / year**		
HFA ≥0 * age	-2.4	0.5	-3.5 – -1.3
HFA <0 and ≥-1 * age	-2.6	0.7	-5.0 – 0.2
HFA <-1 * age	-1.7	0.7	-4.2 – 0.8
Model HFA/TH	***Intercept* FEV_1% pred. age 6**	**Standard Error *b***	**95% Confidence interval**
HFA /TH ≥0	101.5	2.0	97.4 – 105.5
HFA/TH <0 and ≥-1	97.6	2.6	88.4 – 106.8
HFA/TH <-1	97.5	3.0	87.6 – 107.4
	***b* FEV_1% pred. / year**		
HFA/TH ≥0 * age	-2.7	0.5	-3.7 – -1.7
HFA/TH <0 and ≥-1 * age	-1.8	0.6	-4.0 – 0.1
HFA/TH <-1 * age	-2.5	0.7	-4.9 – 0.4

FEV_1% pred. = forced expiratory volume in 1 second % predicted

HFA = z-score height-for-age HFA/TH = height-adjusted-for-target-height

* Corrected for gender, birth cohort, age of diagnose, CF-genotype, meconium ileus

6

Comparison of height-for-age and height-for-bone-age with and without adjustment for target height in paediatric patients with cystic fibrosis

J.W. Woestenenk [1]
T. Hoekstra [1]
C. Hesseling [2]
H.P.J. van der Doef [3]
C.K. van der Ent [2]

[1] Internal Medicine and Dermatology, Dietetics and, Cystic Fibrosis Centre Utrecht, University Medical Centre Utrecht, Utrecht, the Netherlands.
[2] Department of Paediatric Pulmonology, and Cystic Fibrosis Centre Utrecht, University Medical Centre Utrecht, Utrecht, the Netherlands.
[3] Department of Paediatric Gastroenterology, and Cystic Fibrosis Centre Utrecht, University Medical Centre Utrecht, Utrecht, the Netherlands.

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Abstract

Background and aims

Height is a strong prognostic factor in cystic fibrosis (CF) and is usually compared to reference values of healthy children by expressing height as a z-score for height-for-age (HFA). However, HFA does not take into account a potential delay in bone-age (BA) and the genetic potential of the child and could therefore result in misclassification of short stature.

Methods

In 169 children with CF, height, BA and target height (TH) were assessed. HFA, height-for-BA (HBA), HFA-adjusted-for-TH (HFA/TH) and HBA-adjusted-for-TH (HBA/TH) were determined and the children were categorised according to these 4 methods.

Results

Mean z-scores of the 4 methods ranged from -0.1 ± 0.8 (HBA/TH) to -0.5 ± 1.0 (HFA). Prevalence of short stature (z-score <-2) determined by HFA (8%, n = 14) was higher than when HBA, and HFA/TH (both 5%, n = 8) and HBA/TH (1%, n = 1) were applied.

Conclusion

The method used to classify height affects the outcome at the group level and for individual patients. TH and BA are likely to have added value in the interpretation of height in patients with CF.

Introduction

Over the years, survival of patients with cystic fibrosis (CF) has improved dramatically,[1-4] especially in paediatric patients.[5] The increased survival is mainly the result of aggressive treatment of lung disease and increased attention to nutritional status.[1, 6, 7] Along with pulmonary function, nutritional status appears to be an important prognostic indicator in patients with CF because it is a strong predictor of morbidity and mortality.[1, 6, 7] Height at a young age is significantly associated with pulmonary function at a later age.[8] In the 19,000 patients on the US-CF registry, it was observed that both boys and girls with a height below the 5th percentile at the ages of 5 and 7 years had a much higher risk of death compared to taller patients.[9] Therefore, early detection and timely intervention for reduced height is essential to optimise growth and to reduce mortality in children with CF.

In clinical practice, height is compared to reference values of healthy children based on chronological age, by converting it to a z-score for height-for-age (HFA). Although the use of HFA is widely accepted, it has limitations. Firstly, CF is associated with a delay in skeletal maturation,[10, 11] particularly in adolescence.[12] In these situations, the use of HFA might result in misclassification of height. Secondly, height is a hereditable trait that depends on the height of the biological parents and also the child's own development. In the HFA calculation, no adjustment is made for this genetic component.

Therefore, measurements taking both maturation and the genetic potential of the child into account might provide a more appropriate method to monitor the height-growth of a child with CF. The aim of the current study was to investigate the levels of agreement between HFA, height-for-bone-age (HBA), height-adjusted-for-target-height (HFA/ TH) and HBA-adjusted-for-target-height (HBA/ TH) in both the total group of paediatric patients with CF and in paediatric CF patients with short stature (z-score <-2).

Methods

Study population

In a cross-sectional study, 207 unselected Dutch children with proven CF were recruited from the outpatient clinic of Wilhelmina's Children's Hospital, University Medical Centre Utrecht, the Netherlands. All children had a positive sweat test and/or the presence of 2 CF-mutations, combined with clinical signs of CF. Patients were excluded if a hand-wrist x-ray was not available at the time of analysis (n = 37) or if there was incomplete information on parental height (n = 1). Therefore, data of 169 children were included in the final analyses.

The included patients were in clinically stable condition at the time of the measurements. The measurements were part of the annual check-ups and were performed in order to improve the standard of health care. All patients, or parents when it concerned young children, gave informed consent to collect the data in a database. Data was collected between May 2008 and July 2009. The study was performed according to the guidelines of the medical ethics board of the University Medical Centre Utrecht.

Bone-age assessment

An x-ray was performed of the left hand-wrist. Bone-age (BA) was determined, using the method of Greulich and Pyle[13] by a paediatric radiologist and an educated researcher (C.H.) who were blinded to clinical features. If the hand x-ray did not correspond to one standard, BA was defined as age between 2 standards. When the assessment of BA varied less than 1 year between the 2 observers the BA was defined as the mean of both values. In situations where it varied more than a year, the hand-wrist x-ray was interpreted by a third independent paediatric radiologist. If the difference of outcome was less than a year, the mean of the 2 values that were most comparable was defined as BA. A difference of more than a year was discussed by 2 interpreters until consensus was reached.

Target height assessment

During the outpatient visits, the height of the biological parents of the patient were measured with a stadiometer to the nearest 0.5 cm (Holtain, Crymich, UK) and expressed in centimetres. Missing heights were completed by contacting the parent by telephone (n = 6). Target height (TH) was defined as height at age 18 years and calculated with the following formulas: TH *boys = 44.5 + 0.376 x father height + 0.4111 x mother height*; TH *girls = 47.1 + 0.334 x father height + 0.364 x mother height*. Z-scores for TH were calculated using the following formulas: *z-score boys TH boys = (TH - 183.8) / 7.1;* z*-score girls TH = (TH - 170.7) / 6.3*. Formulas for calculating the TH were based on a nationwide growth study in the Netherlands.[14] In 2010, revised growth charts and formulas were published based on most recent data. These formulas adjust for genetic potential in children with discordant parents.[15]

Clinical measurements

Pulmonary function was assessed by forced expiratory volume in 1 second (FEV_1). FEV_1 was obtained from maximal expiratory flow volume curves (Masterscreen, Viasys Healthcare, Höchberg, Germany) and expressed as percentage of predicted for height and sex (FEV_1% pred).[16] A 3-day dietary food record was used to estimate the mean daily caloric intake, expressed as a percentage of the estimated average requirement for healthy Dutch children[17] and protein and fat intake were expressed as a percentage of the total energy intake.
Height was measured with a stadiometer to the nearest 0.5 cm (Holtain, Crymich, UK) and expressed in centimetres. Weight was measured using a digital weight scale to the nearest 0.1 kg. The ratio of weight/height^2 (kg/m2) was used to calculate the body-mass-index (BMI). Height and weight were compared with reference values for Dutch children by converting them to z-scores for HFA, weight-for-age, weight-for-height and BMI, using specialised software (Growth Analyser 3, 2001 – 2004, Dutch Growth Foundation). For non-Dutch children, height was compared to reference values of their nationality. Children with 1 non-Dutch parent were analysed to conform to Dutch growth charts. HBA was determined by using BA instead of chronological age. Both HFA and HBA were additionally adjusted for TH by subtracting z-scores for TH from HFA and HBA, respectively, as previously described in the Dutch Consensus Guideline.[18]
The z-scores for height, defined by the 4 methods, were classified into 4 categories of nutritional status: z-score ≥0, z-score <0 and ≥-1, z-score <-1 and ≥-2 and z-score <-2 (i.e. short stature).

Statistics

The Student's *t*-test for independent samples and the Pearson's chi-square test were performed to compare baseline differences between boys and girls. For the total group and for boys and girls separately, clinical characteristics and anthropometric variables were reported. Comparison between the outcomes of z-scores for height was made for the 4 methods. In addition, the agreement between HFA and HBA, HFA/TH and HBA/TH was assessed by calculating the weighted Cohen's kappa coefficient. Kappa coefficients <0.20, 0.21 – 0.40, 0.41 – 0.60, 0.61 – 0.80 and 0.80 – 1.00 were considered to indicate poor, fair, moderate, good and very good agreement, respectively.[19] Because of the marked changes in anthropometry during puberty[20] and reported delayed BA particularly in adolescents,[10, 11] the data was divided into 2 different age groups: <11 years and ≥11 years to investigate the difference between height expressed as HFA and HBA.

Data management was performed using Excel computer software (Microsoft Excel, 2002). Statistical analyses were performed using the Statistical Package for the Social Sciences computer software (SPSS Inc., version 17, IBM, Chicago, IL). The weighted Cohen's kappa coefficients were calculated using SAS (version 9.1, SAS Institute Inc., Cary, NC, USA).

Results

Study population

This study included 169 children with proven CF. The study population consisted of 162 Dutch children, 2 Moroccan children, 3 Turkish children and 2 children of another nationality. The best recorded FEV_1% pred. during the last year ranged from 25% to 128%. The mean FEV_1% pred. was 90% (± 20%). After classifying the outcomes of the pulmonary function tests, 72% had normal pulmonary function (FEV_1% pred. ≥80%), 20% had moderate pulmonary function (FEV_1% pred. <80% and ≥60%) and 8% had impaired pulmonary function (FEV_1% pred. <60%). The mean daily caloric intake, expressed as a percentage of the estimated average requirement for healthy Dutch children, ranged from 56% to 159%. The mean protein and fat intakes were respectively 13% (± 2%) and 35% (± 6%) of the total energy intake. Boys and girls were similar in age, FEV_1% pred., energy, protein and fat intake and z-scores for nutritional status.

All but 8 patients were treated with pancreatic enzyme replacement therapy. The mean calculated z-scores for all parameters of the nutritional status (height and/or weight containing data) were below 0 in both the whole group as well as in boys and girls separately. The z-scores for height for HFA were: -0.5 (± 1.0), for HBA were: -0.2 (± 0.9), for HFA/TH were: -0.3 (± 0.9) and for HBA/TH were: -0.1 (± 0.8).

In Figure 1 is a scatter plot of chronological age versus BA presented. In 63% of the patients, a delay in BA compared to chronological age was observed with a mean delay of 2.7 months. Of the study population, 18% had a delay of more than 1 year.

After dividing the population into 2 different age groups (children aged <11 years and adolescents aged ≥11 years), the children showed a mean delay in BA of 3.4 months and adolescents showed a mean delay of 2.4 months. The z-scores for HFA and HBA were comparable for children and adolescents, respectively -0.54 (± 1.07) versus -0.44 (± 0.98) for chronological age and -0.17 (± 0.98) versus -0.26 (± 0.90) for BA.

This study found mean heights of 183 ± 7.5 cm (z-score -0.1) and 169 ± 6.9 cm (z-score -0.1), respectively, for the fathers and mothers of the patients. The baseline characteristics are summarised in Table 1, the height characteristics in Table 2.

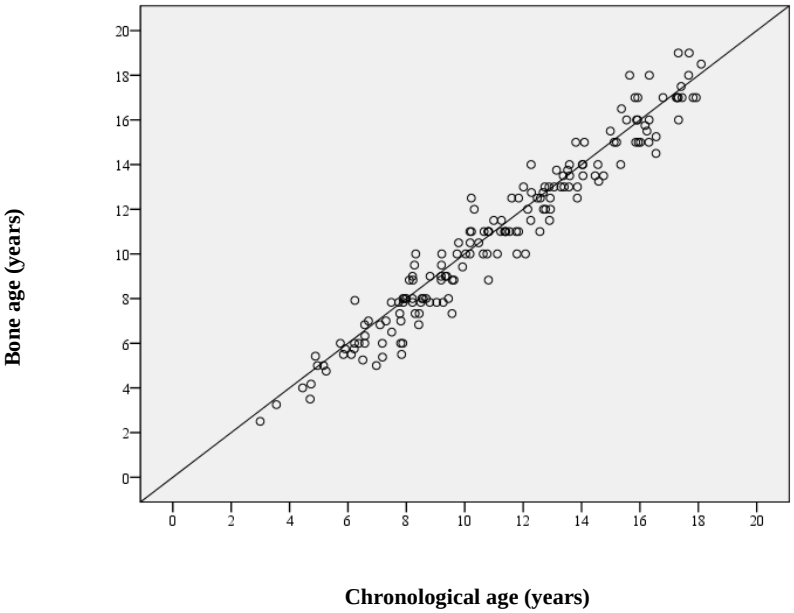

Figure 1. Chronological age versus bone-age in 169 children with cystic fibrosis.
Dots under the line represented a delay in bone-age.

Table 1. Baseline characteristics of the 169 patients with cystic fibrosis.

	Total group (n = 169)	**Boys (n = 90)**	**Girls (n = 79)**	***p*** [a]
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (years)	11.1 ± 3.7	11.6 ± 3.7	10.7 ± 3.6	0.11
Bone-age	10.9 ± 3.7	11.4 ± 4.0	10.3 ± 3.7	0.06
Calculated TH in cm	177 ± 8	183 ± 4	170 ± 4	0.00
Calculated z-score TH	-0.1 ± 0.6	-0.2 ± 0.6	-0.1 ± 0.6	0.75
BMI	17.0 ± 2.2	17.2 ± 2.2	16.9 ± 2.3	0.38
Z-score BMI	-0.3 ± 0.8	-0.3 ± 0.7	-0.4 ± 0.9	0.31
Z-score WFA	-0.5 ± 0.9	-0.5 ± 0.7	-0.5 ± 1.0	0.93
Z-score WFH	-0.3 ± 0.7	-0.2 ± 0.7	-0.3 ± 0.8	0.51
Z-score HFA	-0.5 ± 1.0	-0.6 ± 0.9	-0.4 ± 1.1	0.35
Energy intake (kcal) (n = 139)	2,257 ± 539	2,408 ± 572	2,080 ± 438	0.00
Energy intake (%EAR)	103 ± 20	101 ± 21	104 ± 19	0.40
Protein intake (En%)	13 ± 2	13 ± 3	13 ± 2	0.82
Fat intake (En%)	35 ± 6	35 ± 6	35 ± 5	0.47
CFA (n = 137)	90 ± 8	90 ± 7	89 ± 8	0.93
FEV_1 (% pred)	90 ± 20	91 ± 19	89 ± 20	0.53
CFTR genotype [*] (n)				
Severe	154 (93%)	82 (93%)	72 (92%)	1.00 [#]
Homozygous Δ F508 (%)	105 (63%)	58 (66%)	47 (60%)	0.89 [#]
Mild	12 (7%)	6 (7%)	6 (8%)	

[*] genotype of 3 patients were not identified (2 boys) [a] student *t*-test between boys and girls

[#] Pearson's chi-square test (severe genotype or Δ F508 homozygous versus mild genotype)

TH: target height SD: standard deviation BMI: body-mass-index (kg/m^2)

HFA: height-for-age WFH: weight-for-height WFA: weight-for-age

%EAR: % estimated average requirement En%: percentage of energy intake

FEV_1% pred. = forced expiratory volume in 1 second % predicted

CFA: coefficient of fat absorption

Table 2. Height characteristics of the 169 children with cystic fibrosis (90 boys).

Z-score categories (%)	HFA	HBA	HFA/TH	HBA/TH
≥0	31	41	36	47
<0 and ≥-1	38	38	41	40
<-1 and ≥-2	22	16	18	13
<-2	8	5	5	1

TH: target height HFA: height-for-age HBA: height-for-bone-age
HFA/TH: HFA-adjusted-for-TH HBA/TH: HBA-adjusted-for-TH

Comparison of height for age and bone-age with and without adjustment for target height

The z-scores for height, defined by the 4 methods, were classified into 4 categories: z-score ≥0, z-score <0 and ≥-1, z-score <-1 and ≥-2 and z-score <-2 (i.e. short stature). In Table 3, the distributions over these categories, when using the adjusted methods (i.e. HBA, HFA/TH and HBA/TH), are compared with the distribution when the z-score for HFA was applied. Agreements between outcomes are in bold text and underlined. The highest level of agreement with HFA was observed for the classification using the z-score for HFA/TH. In 104 children (62%), these 2 methods resulted in the same classification (weighted kappa 0.56). For 45 children (27%) using HFA/TH resulted in a higher z-score category than when HFA was used. For HBA in 92 children (54%), agreement was observed with classification according to HFA (weighted kappa 0.47). The largest deviation from the categorisation using HFA was observed for HBA/TH, the measure using both HBA and HFA/TH (weighted kappa 0.26). For only 47% of the children (n = 80) those 2 methods resulted in the same category. For some individual children, differences were distinct. Four children fell in the highest z-score category (z-score ≥0) when HBA/TH was applied, whilst they were categorised in the lowest z-score category (i.e. short stature) when HFA was used. Only 1 child was defined as having short stature by HFA and HBA/TH. Overall, height expressed as HFA resulted in lower z-scores in comparison to the other 3 methods.

Performing the analysis separately for boys and girls yielded comparable results (data not shown).

Table 3. Comparison of the classification of height expressed as z-score for height-for-age (HFA) with z-score for height-for-bone-age (HBA), z-score for HFA-adjusted-for-target-height (HFA/TH) and z-score for HBA-adjusted-for-TH (HBA/TH) in 169 children with cystic fibrosis.

	HBA				**HFA/TH**				**HBA/TH**			
HFA	≥0	<0 and ≥-1	<-1 and ≥-2	<-2	≥0	<0 and ≥-1	<-1 and ≥-2	<-2	≥0	<0 and ≥-1	<-1 and ≥-2	<-2
≥0	**40**	12	1	0	**43**	9	1	0	**38**	12	3	0
<0 and ≥-1	26	**31**	7	0	15	**42**	6	1	26	**32**	6	0
<-1 and ≥-2	3	18	**15**	2	2	18	**15**	3	12	17	**9**	0
<-2	1	3	4	**6**	0	2	8	**4**	4	5	4	**1**

Data are presented as numbers of children in the specific group.

The bold underlined printed numbers show the agreement in classification of height.

Discussion

In our population of patients with CF low to moderate agreement was found between z-scores for HFA and HFA/TH and HBA with and without adjustment for TH. In general, height expressed as HFA resulted in lower z-scores and therefore more children were defined as having short stature in comparison to the other methods. As far as we know no other studies have described and compared HBA and TH in paediatric patients with CF. Correction for TH and/or BA led to discrepant prevalence estimates of short stature (z-score <-2). Compared with the HFA/TH and HBA methods, the HFA method overestimated short stature in 8 and 10 patients, respectively, and in 13 patients compared to the HBA/TH method. However, according to the HBA and HFA/TH methods, respectively 2 and 4 children were classified as having short stature, while the z-score for HFA was >-2. There was agreement in defining short stature for only 1 child according to all 4 methods.

Mid-parental heights are widely used to help assess an individual child's growth, but there may be limitations when no allowance is made for extremes of parental height, as children of very tall or very short parents tend to be less extreme in their height. Talma et al. took these limitations into account by adjusting for genetic potential in children with discordant parents.[15] The importance of accounting for genetic potential when evaluating stature is supported by a large cross-sectional study of 3,306 patients with CF, aged 2 – 18 years. In that

study it was concluded that without adjustment for genetic potential, the prevalence of short stature is underestimated in children with tall parents and overestimated in children with short parents.[21]

The mean z-score for HFA in our population was -0.5 which corresponds with other studies, in which mean height in children with CF ranged from the 25th to the 44th percentile (z-score ≈ -0.2 – -0.7).[8, 22-24] Short stature was defined as z-score <-2, while some other studies defined short stature as height at the <5th percentile (≈ z-score -1.7). In our population we observed in 11.8% of the children a z-score for HFA below the 5th percentile. Consistent with these findings are the results of 2 cross-sectional studies among, respectively, 788 and 4,577 children with CF, in which z-scores beneath the 5th percentile for 12.2% – 19.2% of the population were described.[22, 25] Our study showed that 66% of the children had a z-score for HFA below the average of their calculated z-score for TH, while Zhang et al. reported a z-score for HFA below the average of parental height percentile in 80% of the children with CF.[21] This difference might partly be explained by differences in the way parental height was estimated. In our study, parental height was measured, whilst Zhang et al. used self-reported height. It is known that self-reported height is generally overestimated,[26] resulting in lower z-scores for TH in those parents' children.

BA was determined according to the method of Greulich and Pyle.[13] This method is relatively easy to perform and has been shown to have good reproducibility.[27] It has been questioned whether this method is still valid in modern-day children as it has remained unchanged for more than 50 years. However, it was shown to be still applicable in Dutch Caucasian children and adolescents.[28] The children from the study of Greulich and Pyle were from upper-middle-class homes, which might explain why the reference BA in the atlas have been found to be advanced relative to almost all general populations studied since then. In 63% of the patients, a delay in BA compared to chronological age was observed with a mean delay of 2.7 months. These results are comparable with data from a large study of healthy Dutch children.[28] To our knowledge, only 2 other studies have investigated BA in children with CF. Buntain et al. reported a delay of BA of 2.0 months in children with CF which is comparable to our results. However, they observed a delay of BA of 9.8 months in adolescents with CF, which is more pronounced than our results.[12] Besides the general disease state, they implied that nutritional status had a great impact on skeletal maturation. Our study showed a slightly better nutritional condition of the study population in comparison to the adolescents in the study of Buntain et

al. (z-scores for weight-for-age -0.57 ± 0.79 versus -0.79 ± 0.88, z-scores for HFA -0.44 ± 0.98 versus. -0.91 ± 0.82, respectively). These differences in nutritional status probably explain the differences in skeletal maturation. Another study from 1964 described that BA was delayed by more than 24 months in a quarter of the adolescents with CF.[29] That study is from a time when there was less attention on nutritional intervention and therefore probably a suboptimal nutritional status. The differences in outcome of BA between that study and more recent studies can probably be attributed to the increased attention to nutritional status over the years. Since poor nutritional status may attribute to the delay in BA, it might not be appropriate to adjust for BA in clinical settings. However, children with delayed development might have a prolonged growth potential. More research is needed to be able to draw conclusions on the most valid representation of height.

An important implication can be drawn from the deviation in classifying nutritional status according to the 4 methods. Current guidelines state that children with reduced BMI and/or reduced weight-for-height need high-energy diets, including supplementation with high-energy drinks and/or enteral tube feedings if necessary.[30, 31] Weight-for-height and BMI calculations using unadjusted height, may cause an underestimation of the impact of CF-associated malnutrition because children with short stature and normal weight will still have normal BMI and/or weight-for-height z-scores. This might result in inadequate nutritional treatment in this specific group, and stresses the need to take delays in skeletal maturation and genetic contributions into account when evaluating height as part of the nutritional status assessment.

This study did not include puberty status measurements, because this data was not available. The results of this study may have been affected by this, as the study results were compared with reference values collected in healthy children with normal puberty development.

The main drawback of the study is that it concerns a cross-sectional analysis, so it is not justified to make strong conclusions regarding clinical implications based on the findings. A gold standard for expressing height is not available and it is thus unclear which method would be preferable in clinical practice for children with CF. However, we observed that the method used to classify height affects outcome on a group level and for individual patients. Under current guidelines, unadjusted height is being used which might result in misclassification of short stature. The commonly used method may thus not be the most appropriate method.

However, more research is needed before conclusions can be drawn regarding which method is the most valid. Longitudinal analyses are necessary to relate changes in these measurements over time with clinical outcomes, such as pulmonary status.

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Part 3

Vitamin A and E intake in children and adolescents with cystic fibrosis

7

Vitamin A and E intake in children and adolescents with cystic fibrosis

(Introduction, methods)

J.W. Woestenenk [1]
N. Broos [2]
R.K. Stellato [3]
H.G.M. Arets [2]
C.K. van der Ent [2]
R.H.J. Houwen [4]

[1] Internal Medicine and Dermatology, Dietetics and, Cystic Fibrosis Centre Utrecht, University Medical Centre Utrecht, Utrecht, the Netherlands.
[2] Department of Paediatric Pulmonology, and Cystic Fibrosis Centre Utrecht, University Medical Centre Utrecht, Utrecht, the Netherlands.
[3] Department of Biostatistics, Julius Centre, University Medical Centre Utrecht, Utrecht, the Netherlands.
[4] Department of Paediatric Gastroenterology, and Cystic Fibrosis Centre Utrecht, University Medical Centre Utrecht, Utrecht, the Netherlands.

Introduction

Cystic fibrosis (CF) is a lethal genetic disorder, characterised by chronic pulmonary inflammation that causes a gradual, progressive decline in pulmonary function (PF), partly due to oxidative stress.[1] Most patients in Northern-Europe also have pancreatic insufficiency,[2] leading to intestinal malabsorption of fat and fat-soluble vitamins. Therefore, lifelong treatment with pancreatic enzymes and fat-soluble vitamins such as vitamin A and E has become standard care.[1, 3]

Vitamin A, which plays a role in immune function, vision, reproduction, growth and epithelial cell integrity, is generally routinely administered to all pancreatic insufficient patients, with a recommended daily dosage varying between 1,500 and 10,000 international units.[1, 3] This is considered to be sufficient to prevent deficiency, which indeed has become rare.[4, 5]

Moreover, the vitamin A supplementation may even be too high, as recent studies have reported serum retinol levels above the normal reference range in approximately half of CF patients.[6, 7]

It has been suggested that higher serum retinol and α-tocopherol levels have a protective effect on pulmonary condition in CF.[8-11] However, serum retinol and α-tocopherol levels are compromised during a pulmonary exacerbation and recover with resolution of the inflammation.[9, 10, 12-16] Likewise, chronic pulmonary inflammation may reduce both levels, and the reported association between serum retinol and α-tocopherol levels and PF might be secondary. Consequently, the extent of chronic pulmonary inflammation should be considered when investigating the association between PF and both serum retinol and α-tocopherol. In this respect, immunoglobulin G (IgG), the level of which increases once a chronic infection has set in,[17, 18] might be a good marker.

At present, the relation between vitamin A intake, serum retinol levels and PF are poorly understood as most studies were rather small, encompassed small age ranges, were limited by a cross-sectional design, and lack data on fat malabsorption or inflammation.[6-11, 19] Moreover, little is known about daily practice regarding vitamin E intake and serum α-tocopherol levels in large groups of CF patients, as a previous study was rather small and conducted in a limited age range.[20]

We therefore studied in paediatric CF patients during a 7-year follow-up period:

- the association between vitamin A intake, serum retinol levels, the coefficient of fat absorption (CFA) and serum IgG levels (Chapter 7.1)
- the long-term effect of serum retinol and serum IgG on PF (Chapter 7.2)

- the association between vitamin E intake, the CFA and IgG on α-tocopherol levels, and the long-term effect of serum α-tocopherol and serum IgG on PF (Chapter 7.3).

Methods

Study sample

This retrospective study included Dutch children (born between 1988 and 2013) with proven CF and who received medical care at the CF Centre of the University Medical Centre Utrecht. Each child was confirmed as having CF by a positive sweat test and/or the presence of 2 CF-mutations, as well as clinical signs of CF. Dietary data, serum retinol and α-tocopherol levels were obtained during the annual check-ups. We used data obtained between January 2007 and December 2013 of children and adolescents who were receiving pancreatic enzyme replacement therapy at the time of reporting and who had at least

- a measurement of vitamin A intake (dietary intake plus prescribed supplementation) along with a measurement of serum retinol (Chapter 7.1)
- a measurement of serum retinol and whose PF was measured at 6 years of age and older (Chapter 7.2)
- a measurement of vitamin E intake (dietary intake plus prescribed supplementation) or serum α-tocopherol level (Chapter 7.3).

Excluded were transplant patients. All patients or the parents or guardians of young patients provided written informed consent for the storage and analysis of their data. The study was performed in accordance with the guidelines of the medical ethics board of the University Medical Centre Utrecht.

Dietary intake assessment

All CF patients received written instructions on completing a 3-day dietary food record in which they recorded all food and beverages consumed in portion sizes or weights during 2 weekdays and 1 weekend-day whenever possible. Registered dieticians coded and analysed the food records according a standardised approach, using the Dutch Food Composition Table (2010) of the Dutch Nutrition Centre, and the vitamin A and E intake was calculated for each assessment. The prescribed vitamin A and E supplements, as registered in the medical records, were considered as the vitamin A and E administered.

The vitamin A intake (dietary, prescribed supplementation and total), was expressed as microgramme retinol activity equivalents (µg RAE) which allows direct comparison among

different forms of vitamin A such as retinol and beta-carotene. Vitamin E intake (dietary, prescribed supplementation and total), was expressed as milligramme (mg) α-tocopherol. The vitamin A intake was compared with gender- and age-based Dutch nutritional recommendations and expressed as % of gender- and age-based recommended daily advice (RDA), and as % of age-based tolerable upper intake level for healthy referents (TUL).[21] Additionally, both the vitamin A and E intake were expressed as % of both the European and North-American CF-specific vitamin A and E recommendations.[1, 3]

Clinical measurements

Serum retinol levels, expressed as micromole/litre (µmol/L), and serum α-tocopherol levels, expressed as microgramme/decilitre (µg/dL), were measured once per year and analysed by high-performance liquid chromatography. Serum retinol levels <0.7 µmol/L were considered deficient, and concentrations >3.5 µmol/L toxic.[22] The serum retinol and α-tocopherol outcomes were compared with the reference values for age-equivalent Caucasian healthy controls according the US National Health and Nutrition Examination Survey (NHANES) 2005 – 2006.[23]

A fat balance study was performed to measure the fat excretion in faeces and to calculate the CFA. In conjunction with the 3-day dietary intake assessment, a home-based 72-hour stool collection was obtained, starting on day 2 of the dietary intake assessment and ending 1 day after dietary recording (day 4), to determine the mean faecal fat content of this 3-day collection. The CFA was then calculated from the mean dietary fat intake of the 3-day dietary record and the mean daily faecal fat output and expressed as a percentage.

Serum IgG was also measured once per year and expressed as gramme/litre (g/L).

Pulmonary function, assessed by forced expiratory volume in 1 second (FEV_1), was obtained from maximal expiratory flow-volume curves (Masterscreen, Viasys Healthcare, Höchberg, Germany) and was expressed as the percentage of the predicted value for a given height, age and gender (FEV_1% pred.).[24] For each child, the highest FEV_1% pred. measured in the preceding calendar year (beginning at 6 years of age) was used in the analysis.

Statistics

The descriptive statistics of categorical variables were examined. All continuous variables were tested for normality and skewness. Due to repeated measurements of individual patients at different years of age, the children were stratified according to age year (0 year = birth to <1 year, 1 year = 1 to <2 years, 2 year = 2 to <3 years, etc.) for the cross-sectional analyses.

For longitudinal analyses, the linear mixed-model regression was performed. This model allows inclusion of variable numbers of measurements per child and irregularly timed and missing observations. Statistical analyses were performed using the Statistical Package for the Social Sciences Computer Software (SPSS Inc. version 20, IBM, Chicago, IL).

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7.1

Vitamin A intake and serum retinol levels in children and adolescents with cystic fibrosis

(Abstract, statistics, results, discussion, conclusion)

submitted

Abstract

Aim

Pancreatic insufficient cystic fibrosis (CF) patients receive vitamin A supplementation according to CF-specific recommendations to prevent deficiencies. Whether current recommendations are optimal for preventing both deficiency and toxicity is a subject of debate. We assessed the longitudinal relation between serum retinol levels and appropriate variables.

Methods

We studied vitamin A intake, and the long-term effect of vitamin A intake, the coefficient of fat absorption (CFA) and immunoglobulin G (IgG) on serum retinol levels in 221 paediatrics CF patients during a 7-year follow up period.

Results

Total vitamin A intake, derived from 862 dietary assessments, exceeded the tolerable upper intake level in 30% of the assessments, mainly up to the age of 6 years. Although CF patients failed to meet the CF-specific recommendations, serum retinol deficiency was found in only 17 out of the 862 measurements (2%). Longitudinally, we observed no association to serum retinol levels for the total vitamin A intake, CFA, gender or age, but serum retinol levels were associated with serum IgG levels. Each g/L increase in serum IgG level would result in a 2.49% (95% CI -3.60% to -1.36%) reduction in serum retinol levels.

Conclusion

In this large sample of children and adolescents with CF, serum retinol deficiency was rare despite a lower than recommended intake. However, the TUL is commonly exceeded. A reduction in CF-specific vitamin A supplementation recommendations should be considered.

Statistics

We described the dietary vitamin A intake, the prescribed supplementation and the total vitamin A intake (dietary vitamin A plus prescribed supplementation), expressed as µg retinol activity equivalent (RAE). The total intake was also expressed as a % of both the gender- and age-based recommended daily advice (RDA) and the age-based tolerable upper intake level for healthy referents (TUL). Subsequently, we described the prescribed supplementation, expressed as a % of the lower level (LL) and the upper level (UL) of both the European and North-American CF-specific recommendations. Serum retinol levels, CFA and serum IgG levels were also examined. To assess whether total vitamin A intake was related to serum retinol levels, the children were categorised on the basis of their serum retinol as having a level at the $<50^{th}$ or $>50^{th}$ percentile, or a level between the $<5^{th}$ percentile, between the 5^{th} and 95^{th} percentiles, and the $>95^{th}$ percentile of the US National Health and Nutrition Examination Survey (NHANES). The total vitamin A intake among the categories of serum retinol levels were compared, using the Mann-Whitney test or Kruskal-Wallis test, respectively.

For longitudinal analyses, the linear mixed-model regression was performed to evaluate the effect of total vitamin A intake, CFA, serum IgG, gender and age on serum retinol. Included were fixed effects for total vitamin A intake, CFA, serum IgG, gender and the age of child and a random intercept and random slope for the age of child to account for correlations between measurements within children. In the mixed-model, serum retinol was log-transformed to correct for right-skweness.

Results

Clinical characteristics

Data of 221 patients with proven CF (98% Caucasian, 107 girls) were eligible for inclusion. In these patients, we obtained a total of 862 measurements of vitamin A intake along with serum retinol measurements, 646 CFA measurements, and 565 serum IgG measurements.

Vitamin A intake

The mean total vitamin A intake (dietary vitamin A intake plus prescribed supplementation) in the different age groups was between 1,169 µg and 1,546 µg RAE, providing 187% – 419% RDA, and was relatively stable over the age groups (Figure 1, see also Table 1 for details). As recommendations for daily intake are lower for younger children, at these ages, children were more likely to surpass the RDA. An excessive total vitamin A intake, even above the TUL for healthy subjects, was seen in 30% of the assessments, especially in children up to the age of 6 years. Nevertheless, apart from children below 1 year of age, the mean prescribed supplementation in every year of age was lower than both the European, and the North-American CF-specific vitamin A recommendations.[1, 2] Moreover, in most age groups, mean total vitamin A intake was at the lower limit of the European CF-specific recommendation and far below both the upper limit of the European-, and the North-American recommendation (Table 1).

Clinical measurements

Serum retinol levels were more or less constant over the age groups, with median values between 1.2 µmol/L and 1.6 µmol/L, and within the references values of the NHANES[3] (Figure 2, Table 2). A serum retinol deficiency (value <0.7 µmol/L) was found in 2% of the measurements (17 measurements in 11 children) whereas 0.3% of the measurements (3 measurements in 3 children), showed a toxic value (value >3.5 µmol/L). The children with a deficiency had a total vitamin A intake providing 293% ± 240% of the RDA, while in children with toxic values the total vitamin A intake provided 224% ± 73% of the RDA.
The median CFA varied from 89% to 95%, and median serum IgG levels from 3.9 g/L to 12.7 g/L. In the latter, a gradual increase was seen during the age years (Table 2).

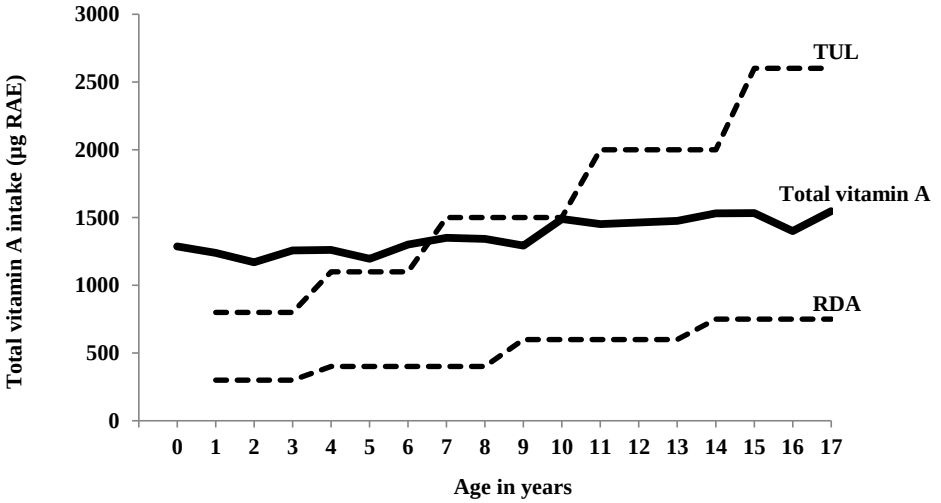

Figure 1. Mean total vitamin A intake (dietary vitamin A intake plus prescribed vitamin A supplementation) expressed as microgramme retinol activity equivalents (µg RAE) per year of age, derived from 862 measurements of 221 patients with cystic fibrosis set out against recommended daily advice (RDA) and tolerable upper intake level (TUL).

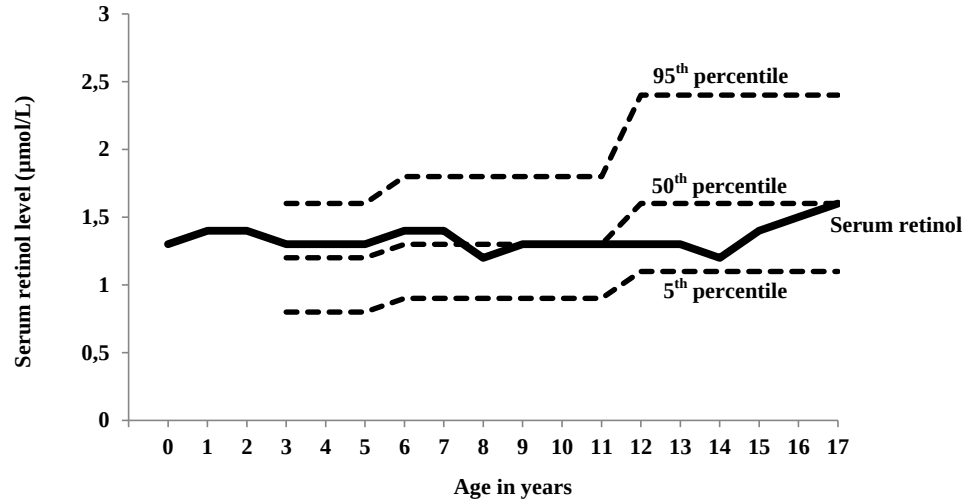

Figure 2. Median serum retinol level, expressed as micromole/litre (µmol/L) per year of age, derived from 862 measurements of 221 patients with cystic fibrosis set out against the US National Health and Nutrition Examination Survey (NHANES) percentiles (dotted lines).

Table 1. Vitamin A intake (dietary intake, prescribed supplementation and total intake) derived from 862 measurements in 221 patients with cystic fibrosis (CF) expressed as microgramme retinol activity equivalents (µg RAE). The total intake is also expressed as a % of the recommended daily advice and tolerable upper intake level of vitamin A intake. The prescribed supplementation is also expressed as a % of both the European and North-American CF-specific vitamin A recommendations.

Age	N	CF-recommendation supplementation						Dietary intake	Supple-mentation
				EU		US			
		RDA	TUL	LL	UL	LL	UL	µg RAE	µg RAE
0	11	nd	nd	1,200	3,000	450		548 ± 137	739 ± 628
1	26	300	800	1,200	3,000	1,500		607 ± 273	645 ± 545
2	24	300	800	1,200	3,000	1,500		596 ± 268	573 ± 461
3	35	300	800	1,200	3,000	1,500		599 ± 333	658 ± 648
4	38	400	1,100	1,200	3,000	1,500	3,000	645 ± 283	615 ± 578
5	42	400	1,100	1,200	3,000	1,500	3,000	725 ± 263	471 ± 485
6	46	400	1,100	1,200	3,000	1,500	3,000	814 ± 365	488 ± 451
7	50	400	1,500	1,200	3,000	1,500	3,000	849 ± 357	501 ± 547
8	56	400	1,500	1,200	3,000	3,000		906 ± 414	441 ± 352
9	62	600	1,500	1,200	3,000	3,000		883 ± 440	416 ± 354
10	71	600	1,500	1,200	3,000	3,000		1,014 ± 543	474 ± 477
11	71	600	2,000	1,200	3,000	3,000		1,015 ± 490	442 ± 371
12	73	600	2,000	1,200	3,000	3,000		1,002 ± 436	445 ± 414
13	68	600	2,000	1,200	3,000	3,000		1,068 ± 524	406 ± 292
14	55	750 ‡	2,000	1,200	3,000	3,000		1,141 ± 581	415 ± 392
15	47	750 ‡	2,600	1,200	3,000	3,000		1,126 ± 617	406 ± 328
16	48	750 ‡	2,600	1,200	3,000	3,000		993 ± 539	406 ± 386
17	39	750 ‡	2,600	1,200	3,000	3,000		1,131 ± 655	416 ± 445

RDA: recommended daily advice RAE: retinol activity equivalent LL: lower limit

‡ RDA girls (700 µg) and boys (800 µg) averaged

Table 1. Continued.

Age	N	Total intake			Prescribed supplementation as % of CF-specific recommendations			
					EU		US	
		µg RAE	%RDA	%TUL	LL	UL	LL	UL
0	11	1,287 ± 612			62 ± 52	25 ± 21	164 ± 140	
1	26	1,238 ± 598	413 ± 199	155 ± 74	54 ± 45	21 ± 18	43 ± 36	
2	24	1,169 ± 500	390 ± 167	146 ± 63	45 ± 38	19 ± 15	38 ± 31	
3	35	1,256 ± 651	419 ± 217	157 ± 81	55 ± 54	22 ± 22	44 ± 43	
4	38	1,260 ± 580	315 ± 145	115 ± 53	51 ± 48	21 ± 19	41 ± 39	21 ± 19
5	42	1,196 ± 539	299 ± 135	109 ± 49	39 ± 40	16 ± 16	31 ± 31	16 ± 16
6	46	1,301 ± 546	325 ± 136	117 ± 49	41 ± 38	16 ± 15	33 ± 30	16 ± 15
7	50	1,350 ± 605	337 ± 151	91 ± 41	42 ± 46	17 ± 18	33 ± 36	17 ± 18
8	56	1,343 ± 503	336 ± 126	90 ± 34	37 ± 29	15 ± 12	15 ± 12	
9	62	1,293 ± 520	216 ± 87	86 ± 35	35 ± 30	14 ± 12	14 ± 12	
10	71	1,488 ± 738	248 ± 123	99 ± 49	39 ± 40	16 ± 15	16 ± 15	
11	71	1,451 ± 637	242 ± 106	73 ± 32	37 ± 31	15 ± 12	15 ± 12	
12	73	1,464 ± 671	244 ± 112	73 ± 34	37 ± 35	15 ± 14	15 ± 14	
13	68	1,474 ± 725	244 ± 122	74 ± 36	34 ± 24	14 ± 10	14 ± 10	
14	55	1,530 ± 652	204 ± 86	75 ± 32	35 ± 33	14 ± 13	14 ± 13	
15	47	1,532 ± 797	204 ± 108	61 ± 36	34 ± 27	14 ± 11	14 ± 11	
16	48	1,399 ± 659	187 ± 90	54 ± 25	34 ± 32	14 ± 13	14 ± 13	
17	39	1,546 ± 817	203 ± 107	59 ± 31	35 ± 37	14 ± 15	14 ± 15	

UL: upper limit TUL = tolerable upper intake level nd = not defined

Table 2. Serum retinol levels, coefficient of fat absorption (CFA), immunoglobulin G (IgG), z-scores for weight-for-age (WFA), height-for-age (HFA) and weight-for-height (WFH), derived from 862 measurements of 221 patients with cystic fibrosis.

Age	N (girls)	Serum retinol (µmol/L) *	CFA (%) *
0	11 (7)	1.3 (1.1 – 1.7)	95 (n = 3)
1	26 (12)	1.4 (1.2 – 1.5)	94 (90 – 95) (n = 8)
2	24 (13)	1.4 (1.1 – 1.6)	92 (85 – 94) (n = 6)
3	35 (23)	1.3 (1.1 – 1.5)	91 (85 – 96) (n = 20)
4	38 (21)	1.3 (1.1 – 1.5)	91 (86 – 94) (n = 31)
5	42 (20)	1.3 (1.0 – 1.5)	91 (86 – 96) (n = 32)
6	46 (19)	1.4 (1.2 – 1.6)	89 (86 – 94) (n = 37)
7	50 (25)	1.4 (1.1 – 1.7)	92 (85 – 94) (n = 44)
8	56 (24)	1.2 (1.0 – 1.5)	92 (89 – 95) (n = 49)
9	62 (30)	1.3 (1.1 – 1.4)	90 (85 – 95) (n = 51)
10	71 (33)	1.3 (1.0 – 1.6)	92 (88 – 95) (n = 61)
11	71 (36)	1.3 (1.1 – 1.4)	92 (88 – 95) (n = 58)
12	73 (37)	1.3 (0.9 – 1.5)	91 (87 – 95) (n = 59)
13	68 (39)	1.3 (1.1 – 1.7)	93 (89 – 96) (n = 56)
14	55 (27)	1.2 (1.1 – 1.7)	93 (87 – 96) (n = 43)
15	47 (23)	1.4 (1.2 – 1.8)	92 (89 – 95) (n = 30)
16	48 (23)	1.5 (1.2 – 1.8)	90 (84 – 93) (n = 33)
17	39 (14)	1.6 (1.2 – 2.0)	90 (83 – 93) (n = 25)

* median (25^{th} – 75^{th} percentiles) ** mean ± SD

Table 2. Continued.

Age	N (girls)	IgG (g/L) *	z-score WFA **	z-score HFA **	z-score WFH **
0	11 (7)	3.9 (2.9 – 7.1) (n = 4)	-0.3 ± 1.0	-0.4 ± 1.1	-0.0 ± 0.6
1	26 (12)	5.7 (4.8 – 8.2) (n = 10)	-0.9 ± 0.9	-0.6 ± 0.9	-0.6 ± 0.8
2	24 (13)	6.8 (5.1 – 7.4) (n = 17)	-0.7 ± 1.0	-0.6 ± 0.9	-0.5 ± 1.2
3	35 (23)	6.5 (5.2 – 7.3) (n = 23)	-0.1 ± 0.9	-0.3 ± 0.8	0.1 ± 1.0
4	38 (21)	7.5 (6.5 – 10.0) (n = 22)	-0.3 ± 1.0	-0.5 ± 1.1	0.1 ± 1.0
5	42 (20)	7.5 (6.7 – 9.7) (n = 28)	-0.4 ± 1.1	-0.5 ± 1.1	-0.3 ± 1.0
6	46 (19)	8.0 (6.3 – 10.2) (n = 29)	-0.3 ± 1.0	-0.5 ± 1.0	-0.2 ± 1.0
7	50 (25)	9.1 (6.8 – 11.3) (n = 36)	-0.1 ± 1.0	-0.5 ± 1.0	0.2 ± 0.8
8	56 (24)	9.1 (6.5 – 10.9) (n = 34)	-0.2 ± 0.9	-0.6 ± 1.0	0.1 ± 0.8
9	62 (30)	9.6 (7.9 – 12.5) (n = 41)	-0.2 ± 0.9	-0.5 ± 1.0	-0.0 ± 0.9
10	71 (33)	10.8 (7.2 – 12.6) (n = 46)	-0.2 ± 0.9	-0.6 ± 1.0	-0.0 ± 0.9
11	71 (36)	11.0 (8.1 – 12.0) (n = 41)	-0.2 ± 0.9	-0.5 ± 1.0	-0.1 ± 0.8
12	73 (37)	11.0 (8.4 – 13.2) (n = 56)	-0.4 ± 1.0	-0.6 ± 1.0	-0.1 ± 0.8
13	68 (39)	10.5 (8.0 – 13.2) (n = 46)	-0.4 ± 0.9	-0.4 ± 0.9	-0.2 ± 0.7
14	55 (27)	10.8 (9.2 – 14.6) (n = 36)	-0.3 ± 0.8	-0.5 ± 1.0	-0.0 ± 0.7
15	47 (23)	12.0 (9.7 – 13.9) (n = 32)	-0.4 ± 0.8	-0.4 ± 0.9	0.0 ± 0.7
16	48 (23)	12.7 (10.8 – 14.4) (n = 33)	-0.3 ± 0.7	-0.5 ± 0.7	0.3 ± 0.7
17	39 (14)	12.1 (10.6 – 15.5) (n = 31)	-0.1 ± 0.8	-0.5 ± 0.9	0.6 ± 0.7

Vitamin A intake and serum retinol levels

The children were categorised, for every year of age, into those having a serum retinol level at the <50th or >50th percentile of the NHANES levels at the same age to assess whether a higher vitamin A intake was related to higher serum retinol levels. We found no differences in total vitamin A intake between patients at the <50th or >50th percentile. The exception was at the age of 16; the total vitamin A intake was significantly higher in those with serum retinol levels at the <50th percentile (p=0.046) (Figure 3). After categorising the patients as having a serum retinol level at the <5th percentile, between the 5th and 95th percentiles, or the >95th percentile, we found no differences in the total vitamin A intake among the categories (all p≥0.088). Longitudinally, we found no significant association of serum retinol levels with the total vitamin A intake (95% CI -0.04% to 0.01%, p=0.245) or CFA (95% CI -39.98% to 55.83%, p=0.890) but serum retinol levels were associated with serum IgG levels. Each g/L increase in the serum IgG level would result in a 2.49% (95% CI -3.60% to -1.36%) reduction in the serum retinol level. The relatively large confidence interval for the effect of the CFA indicated a high variability among individuals.

Discussion

The current study in this large sample of children and adolescents with CF showed that the dietary vitamin A intake exceeded the RDA in all age groups. The total vitamin A intake (dietary vitamin A plus prescribed supplementation) exceeded the TUL for healthy subjects in 30% of the assessments, primarily before 6 years of age. Although the vitamin A intake failed to achieve both the European and the North-American CF-specific vitamin A recommendations, serum retinol deficiency was rare. Longitudinally, no association between total vitamin A intake, CFA, gender or age with serum retinol was found but decreasing serum retinol was associated with increasing serum IgG.

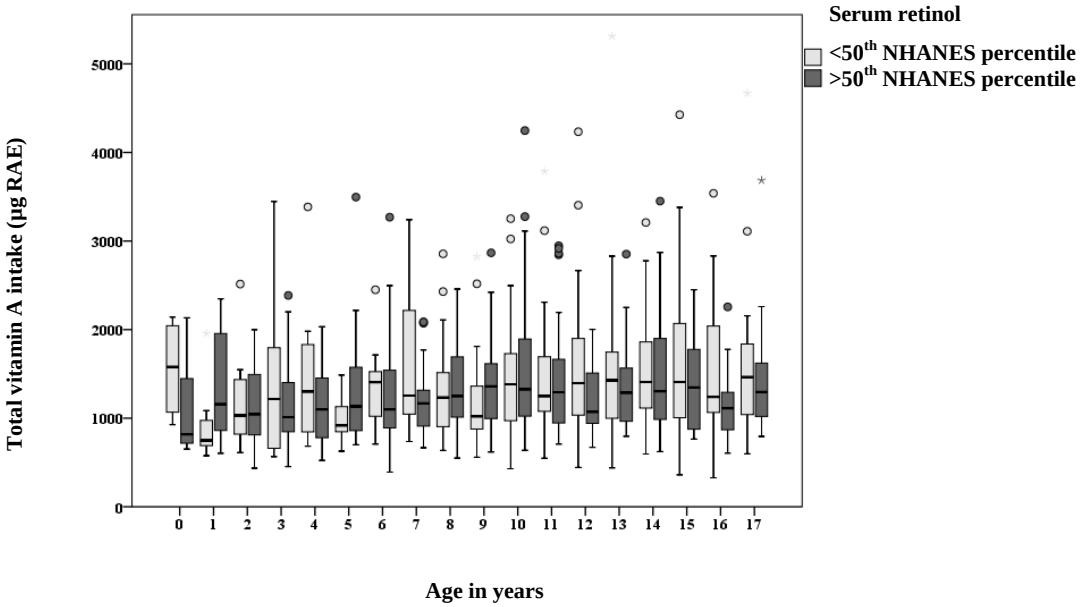

Figure 3. Total vitamin A intake (dietary intake plus prescribed vitamin A supplementation), expressed as microgramme retinol activity equivalents (µg RAE) per year of age, categorised for serum retinol levels at the <50th or >50th percentile (according to the normal reference range of the US National Health and Nutrition Examination Survey (NHANES)) derived from 862 measurements of 221 patients with cystic fibrosis.

In this study we found an excessive vitamin A intake in patients with CF in all years of age, which supports previous results of smaller studies including smaller age ranges.[4-6] This excessive intake poses a risk of vitamin A toxicity as the body stores excess vitamin A, primarily in the liver. This stored retinol is potentially toxic. Although the current study mainly found serum retinol levels within reference ranges, it is unknown whether excessive hepatic retinol levels were present. The best way to determine an abnormal vitamin A status is through hepatic biopsy; however, this invasive procedure is unsuitable for population studies and the assessment of serum retinol levels is a generally accepted method for large clinical studies.

Moreover, serum retinol levels were not significantly dependent on the vitamin A intake, as has also been found by others.[5,6] Nevertheless, 2 cross-sectional studies from the United Stated, including 73 and 78 CF patients in an older age range (8 years up to 12 and 25 years, respectively), found high serum retinol levels in patients with extremely high vitamin A intakes, in which, respectively, 49% and 73% of the patients exceeded the current

recommendations.[4,6] The observation of high serum retinol levels in these cohorts suggest a causal relationship, although a direct correlation could not be found.[6] It is possible that with a moderate vitamin A intake, as was found in our study, the correlation with serum retinol levels is minimal or non-existent, while with very high intakes serum retinol levels might indeed be boosted to above normal levels.

In our cohort, the current CF-specific recommendations for vitamin A intake were only met in the infants. Nevertheless, median serum retinol levels were within the references values of the NHANES at all ages. Moreover, a comparable number of patients had serum retinol levels at the $<5^{th}$ or $>95^{th}$ NHANES percentile. The vitamin A intake achieved in our cohort seems to be sufficient to maintain a normal serum retinol level, as was also found in another European study.[4] This was surprising, since the supplementation prescribed was only half or less of the current recommendations. In addition, the mean total vitamin A intake was in the bottom of the lower limit of the European CF-specific recommendation and far below both the upper limit of the European and North-American CF-specific recommendations. This suggests that both the European and North-American CF-specific recommendations for vitamin A intake are higher than necessary to prevent deficiencies and may even lead to excessive vitamin A intake. Moreover, not only in our study, but especially in 2 American studies,[5, 6] many patients exceeded the TUL, considered the maximum daily intake above which toxicity in healthy children might be seen. It seems therefore appropriate to reduce the recommendations for vitamin A supplementation in CF, at least in infants and young children.

We found no association between the CFA and serum retinol levels, which is in line with a study in CF patients in whom identical serum retinol levels were found in both pancreatic sufficient and pancreas insufficient patients.[7] Previously, a serum retinol deficiency was described in patients with severe steatorrhoea, but in our study and others[8] (near) normal CFA were encountered, suggesting that the fat malabsorption is most often well-treated and therefore reducing the loss of fat-soluble vitamins. This enables a potential effect on retinol levels hard to detect. In healthy people serum retinol levels are reduced by 11% to 24% during an infection, as a result of the increased consumption of the retinol and recover subsequently.[9] Likely, in patients with CF, serum retinol concentrations are transiently depressed during acute inflammation.[10-12] Indeed, we found a gradual increase in serum IgG levels during the age years. These higher IgG levels were associated with declined serum retinol levels which may have been the result of an increased incidence of the chronic pulmonary inflammation

with increasing age, as found by others.[10] It can be assumed that a lowering in serum retinol levels might be due to the acute inflammation rather than a nutritional vitamin A deficiency as we observed no significant correlation between serum retinol levels and total vitamin A intake.

Because this was a single centre study, the results might not be generalised to other CF-centres and populations. Moreover, keeping food records can be burdensome, leading to alterations of the diet and to over- and/or under-reporting, which affects the validity. Further, we did not subjected to objective measure the adherence to vitamin supplementation, which could lead to an overestimation of the true total vitamin A intake. The commonly used vitamin supplementation contains water-miscible vitamin A, although the use of other vitamin supplement products was not ruled out and thus may affected the calculated vitamin A intake. Also taking additional supplements containing vitamin A or vitamin A enriched food, which had not been reported by patients, may underestimate the vitamin A intake in the present study.

Conclusions

In this large sample of children and adolescent with CF, the current recommendations for vitamin A supplementation in CF were not met. Nevertheless, the serum retinol distribution was normal. It seems that the current vitamin A specific recommendations are no longer appropriate and a reduction in CF-specific vitamin A supplementation recommendations should therefore be considered.

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7.2

Serum retinol levels and pulmonary function in children and adolescents with cystic fibrosis

(Abstract, statistics, results, discussion, conclusion)

Journal of Cystic Fibrosis. In press

Abstract

Background

It has been suggested that higher serum retinol levels have protective effects on pulmonary function (PF) in patients with cystic fibrosis (CF). However, serum retinol levels will be transiently decreased during pulmonary exacerbation. Therefore, the extent of chronic pulmonary inflammation should be included when describing the association between PF and serum retinol. We assessed the longitudinal relationship between serum retinol, immunoglobulin G (IgG) and PF in paediatric CF patients.

Methods

We studied serum retinol, IgG and forced expiratory volumes in 1 second (FEV_1% pred.) of 228 CF patients during a 7-year follow up period. The cross-sectional and longitudinal relations between these variables were assessed.

Results

Serum retinol, with medians levels between 1.2 µmol/l and 1.4 µmol/l, were relatively stable, while median serum IgG gradually increased during the age years. The FEV_1% pred. was longitudinally inversely associated with serum IgG and age, but not with serum retinol. Each g/L increase in serum IgG level was associated with an accelerated yearly decline in FEV_1% pred. of 0.5% (95% CI -0.8% to -0.1%, p=0.008), and each year increase in age was associated with a 1.7% (95% CI -2.1% to -1.3%, p=0.000) decline in FEV_1% pred. This effect was not observed with respect to serum retinol levels (95% CI -1.9 g/L to 2.2 g/L, p=0.570).

Conclusions

In this large sample of children and adolescents with CF, we found no evidence that higher serum retinol levels had protective effects on PF.

Statistics

Serum retinol levels, serum IgG levels and FEV_1% pred. for each year of age were described. The cross-sectional relationships between serum retinol levels, serum IgG levels and FEV_1% pred. were determined for each age group.

We then assessed if higher serum retinol levels were associated with a better PF. For this purpose, the children were categorised, based on their serum retinol levels as having a level at the $<50^{th}$ or $>50^{th}$ percentile, or a level at the $<2.5^{th}$, between the 2.5^{th} and 50^{th} percentiles, between the 50^{th} and 97.5^{th} percentiles, or the $>97.5^{th}$ percentile of the US National Health and Nutrition Examination Survey (NHANES). The mean FEV_1% pred. outcomes among the categories of serum retinol levels were compared, using Mann-Whitney test and Kruskal-Wallis test, respectively.

Subsequently, we examined if higher serum IgG levels were associated with lower PF. Based on their IgG level, the children were categorised into those having a serum IgG level at the $<50^{th}$ or $>50^{th}$ percentile, or as having a level at the $<2.5^{th}$ percentile, between the 2.5^{th} and 50^{th} percentiles, between the 50^{th} and 97.5^{th} percentiles or the $>97.5^{th}$ percentile of the paediatric reference intervals for Caucasian children. We compared the mean FEV_1% pred. outcomes among the categories of serum IgG levels, also by using Mann-Whitney test and Kruskal-Wallis test, respectively.

For longitudinal analyses, the linear mixed-model regression was performed to evaluate the effect of serum retinol and serum IgG on FEV_1% pred. Included were fixed effects for serum retinol, serum IgG and the age of the child and a random intercept and random slope for the age of child to account for correlations between measurements within children.

Results

A total of 228 patients with proven CF (98% Caucasian) were eligible for inclusion. In these patients, we obtained a total of 1,033 serum retinol measurements, 669 IgG measurements, and 846 FEV_1% pred. measurements.

Serum retinol levels

The serum retinol levels were more or less constant over the age groups, with median levels between 1.2 µmol/l and 1.4 µmol/l. However, when serum retinol levels were set out against the NHANES percentiles, the median level falls below the 50^{th} percentile in children 8 years and older (Figure 1, see also Supplemental Table 1).

We found no association between serum retinol levels and FEV_1% pred. in the different age groups (correlations between -0.164 and 0.275, Supplemental Table 1). For further analyses, the children were categorised, for each year of age, as having a serum retinol level at the <50th or >50th percentile of the NHANES. The mean FEV_1% pred. outcomes between the serum retinol categories were examined and, aside from age group 6 (p=0.029), the distribution of FEV_1% pred. across the serum retinol categories did not differ (all p≥0.070) (Figure 2, see also Supplemental Table 2a, 2b for detailed information).

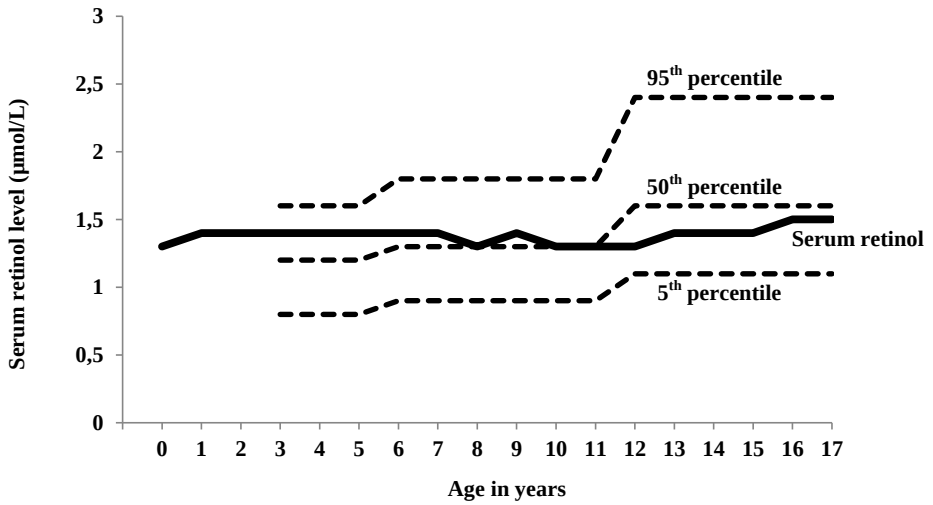

Figure 1. Median serum retinol levels, expressed as micromole/litre (µmol/l) per year of age, derived from 1,033 dietary measurements of 228 patients with cystic fibrosis set out against the US National Health and Nutrition Examination Survey (NHANES) percentiles (dotted lines).

The children were also categorised as having a serum retinol level at the <2.5th percentile, between the 2.5th and 50th percentiles, between the 50th and 97.5th percentiles or the >97.5th percentile of the NHANES in which we again found no differences in FEV_1% pred. distribution among the categories (all p≥0.077) (Supplemental Table 2a, 2b). A different categorisation of serum retinol, between the 2.5th and 97.5th percentiles and the >97.5th percentile, did not change these results (all p≥0.150) (data not shown).

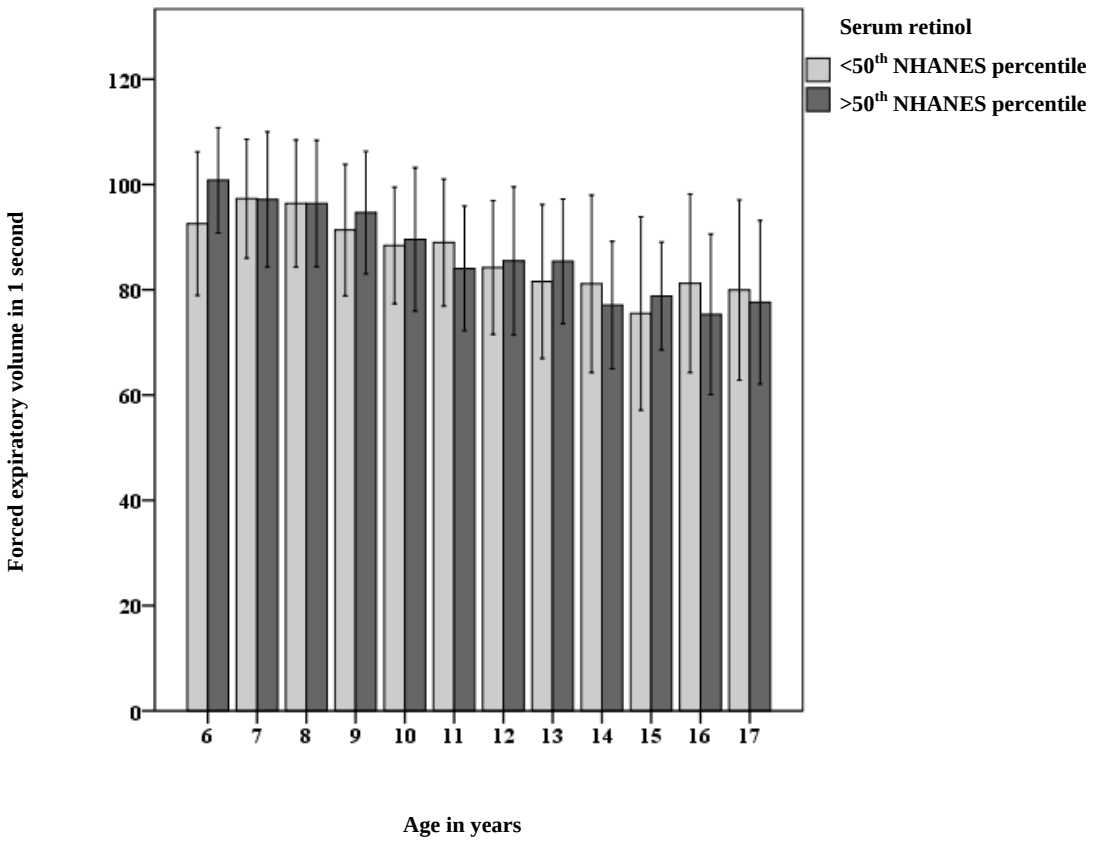

Figure 2. Mean forced expiratory volume in 1 second (FEV_1% predicted, ± 1 SD) per year of age, categorised for serum retinol levels at the < 50th or >50th percentile (according to the normal reference range of the US National Health and Nutrition Examination Survey (NHANES)) derived from 846 measurements of 198 patients with cystic fibrosis.

Serum IgG levels

Median serum IgG levels varied, except in the group below 1 year of age, between 6.1 g/L and 13.1 g/L. A gradual increase was seen during the age years, with values above the 50th percentile of the paediatric reference intervals for Caucasian children in the older age groups (Figure 3, see also Supplemental Table 1).

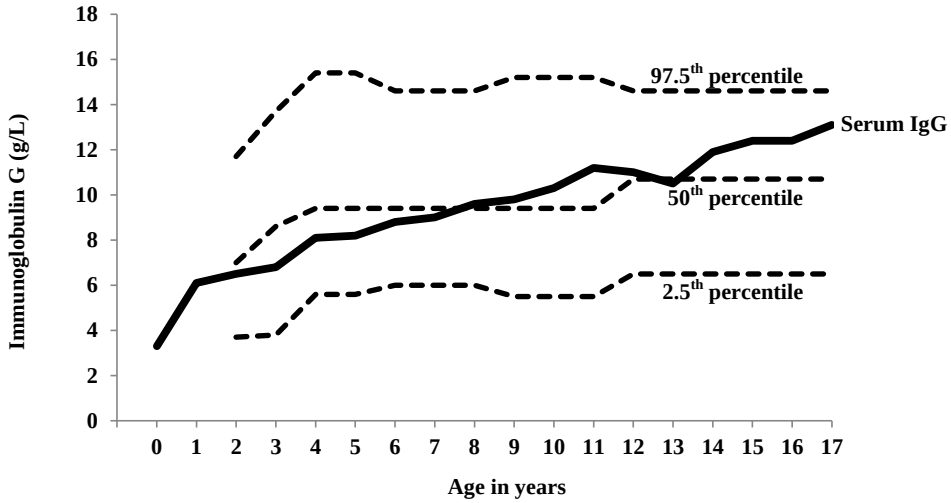

Figure 3. Median serum Immunoglobulin G (IgG) levels, expressed as gramme/litre (g/L) per year of age, derived from 669 dietary measurements of 228 patients with cystic fibrosis set out against the reference percentiles for Caucasian children (dotted lines).

Patients were stratified according to the age year and, overall, an inverse relation between IgG level and FEV_1% pred. was found, i.e. within an age group higher IgG levels were generally related with lower FEV_1% pred. Moreover, we found that higher IgG levels were associated with lower serum retinol levels (see Supplemental Table 1 for details).

Subsequently, the children were categorised, for each year of age, as having a serum IgG level at the $<50^{th}$ or $>50^{th}$ percentile, and also as having a level at the $<2.5^{th}$, between the 2.5^{th} and 50^{th} percentiles, between the 50^{th} and 95^{th} percentiles or the $>97.5^{th}$ percentile of the paediatric reference intervals for Caucasian children. The FEV_1% pred. outcomes among the IgG categories were examined. We found that patients with serum IgG levels at the lower percentile groups generally had higher FEV_1% pred. than those with serum IgG levels at the higher percentile groups, which became particularly clear in the older age groups (Figure 4, see also Supplemental Table 3a, 3b for detailed information).

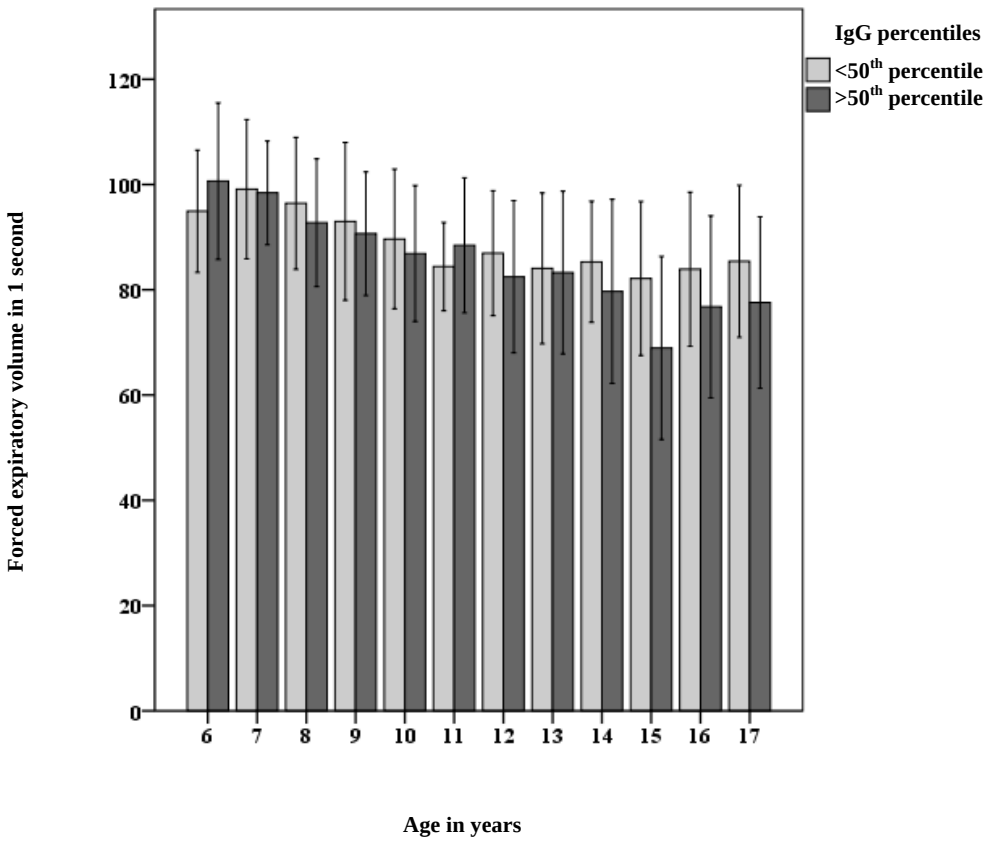

Figure 4. Mean forced expiratory volume in 1 second (FEV_1% predicted, ± 1 SD) per year of age, categorised for serum immunoglobulin G (IgG) levels at the <50th or >50th percentile (according to the paediatric reference intervals for Caucasian children) derived from 564 measurements of 190 patients with cystic fibrosis.

Longitudinally, FEV_1% pred. was significantly associated with serum IgG and age, but not with serum retinol. Each g/L increase in serum IgG level was associated with an accelerated yearly decline in FEV_1% pred. of 0.5% (95% CI -0.8% to -0.1%, p=0.008) and each year increase in age was associated with a 1.7% (95% CI -2.1% to -1.3%, p=0.000) decline in FEV_1% pred. This effect was not observed with respect to serum retinol levels (95% CI -1.9 g/L to 2.2 g/L, p=0.570).

Discussion

In the current longitudinal study, we found no association between serum retinol levels and FEV_1% pred., but the FEV_1% pred. was inversely associated with age and serum IgG levels. In this large patient cohort we obtained no evidence that higher serum retinol levels have protective effects on PF in patients with CF, which is consistent with 2 previous studies,[1, 2] but contrasts with the findings in 4 studies that report a correlation between FEV_1% pred. and serum retinol levels.[3-6] However, in 2 out of these 4 studies,[4, 5] serum retinol levels were at least partially measured during an acute exacerbation. This may yield deceptively low levels, as it is known that pulmonary inflammation leads to a transient decrease of these levels.[2, 4, 5, 7, 8] Moreover, the age ranges in both these studies differed from our study: respectively 1 – 27 years of age[4] and 1 – 45 years of age[5] versus 0 – 18 years of age in our cohort. Consequently, an association between a low serum retinol and a compromised PF might be present in adults with a severely reduced FEV_1% pred., which we were unable to study. In a small study of 38 CF patients with ages between 6 and 25 years, in whom an acute inflammation was excluded, a significant correlation between serum vitamin A and FEV_1% pred. ($p=0.02$) was found.[3] However, in 13 out of these 38 patients (34%), the serum retinol levels were below the reference range for the general population, which suggests a relation between subnormal retinol levels and FEV_1%pred, instead of a general effect. Moreover, in that study[3] information on an inflammation marker was lacking, so the possibility that the observed correlation may have been – partly – due to the presence of chronic recurrent pulmonary inflammation rather than to serum retinol levels cannot be excluded.

The other study, by Rivas-Crespo et al. was a cross-sectional study of FEV_1% pred. in 98 clinical stable CF patients, aged 6 – 22 years.[6] Despite the large age range, these patients were pooled and categorised based on their serum retinol levels in those having a serum retinol level between the 2.5^{th} and 97.5^{th} percentiles, or at the $>97.5^{th}$ percentile of the NHANES. Those having a serum retinol at the $>97.5^{th}$ percentile had a better FEV_1% pred. ($p<0.05$), but were also significantly younger ($p<0.05$) than those having a serum retinol level between the 2.5^{th} and 97.5^{th} percentiles. The observed effect may in fact have been the result of the average yearly progressive decline in FEV_1% pred. and the more severe chronic inflammation that is seen with increasing age. Indeed, we found that higher IgG levels were associated with an accelerated decline in FEV_1% pred. which is in line with previous studies.[9, 10]

In healthy people serum retinol levels are reduced by 11% to 24% during an infection, as a result of the increased consumption of retinol, and recover subsequently.[8] A similar situation seems to exist in patients with CF, as serum retinol concentrations are depressed during acute inflammation with recovery afterwards.[2, 4, 5, 7] In addition, we and others[7] have found a relative decline – i.e. with respect to controls – of serum retinol with increasing age, which might be due to an increased incidence of chronic pulmonary inflammation with increasing age. Indeed, we found a gradual increase of IgG for each year of age, and an inverse relation between serum retinol levels and IgG levels. Chronic pulmonary infection may also render CF patients at risk for subnormal serum retinol levels, as was found in a substantial proportion of the patients studied by Aird et al.,[3] although not in our population.

Almost all patients included in this study had serum retinol levels within the normal NHANES reference ranges. Therefore this study lacks the numbers to reliably exclude a protective effect of supranormal serum retinol levels on PF decline. Nevertheless, within the serum retinol distribution as seen in our cohort we found no effect on the trend in PF whatsoever. In addition, only few patients in our study had a severely decreased PF. A potentially protective effect of serum retinol, when FEV_1 is already severely compromised, could therefore not be reliably assessed. Only few studies did address this question.[1, 4, 6] Five patients included in the study of Rivas et al. with a FEV_1 pred. below 60% had mean serum retinol levels only slightly below normal[6] while 5 patients of the Brei study, with a similar low FEV_1 pred., had serum retinol levels around z-score -1.[1] The latter found no direct correlation between PF and serum retinol, although those with lower serum retinol levels had significantly elevated serum IgG levels ($p=0.017$).[1] Hakim et al. included 8 patients with a FEV_1 pred. below 60%, who all had a low serum retinol level, but also frequent pulmonary infections.[4] So these studies in patients with a severely compromised PF do not contradict our suggestion that a low serum retinol is primarily caused by frequent or persistent pulmonary infections.

In this study we did not find protective effects of serum retinol on pulmonary function, yet substantial dietary supplementation of this vitamin is generally advised for pancreatic insufficient CF patients.[11, 12] Several studies now show that this will result in serum retinol levels above the normal reference range, which is potentially toxic.[13, 14] Moreover, vitamin A supplementation at half or less the current recommendations still resulted in adequate serum retinol levels.[1] Given this result, and the lack of evidence for beneficial effects of high serum

retinol levels, it might be advisable to reduce current CF-specific vitamin A recommendations.

Conclusion

In this large sample of children and adolescent with CF, we found no evidence that higher serum retinol levels had protective effects on PF. However, a higher serum IgG level, indicating chronic inflammation, was seen in patients with a more pronounced yearly decline in FEV_1% pred.

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Supplemental Table 1. Forced expiratory volume in 1 second expressed as percentage of predicted (FEV_1% pred.), serum retinol levels and immunoglobulin G (IgG) levels, derived from 1,033 measurements of 228 patients with cystic fibrosis and their relationship.

Age	N	Serum retinol (µmol/L) Mean ± SD (median)	IgG (g/L) Mean ± SD (median)	FEV_1 (% pred.) Mean ± SD	*r* FEV_1 serum retinol	*r* FEV_1 IgG	*r* serum retinol IgG
0	8	1.3 ± 0.3 (1.3)	3.3 ± 1.0 (3.3) (n = 2)				
1	28	1.4 ± 0.4 (1.4)	6.1 ± 2.3 (5.7) (n = 12)				-0.134
2	28	1.4 ± 0.5 (1.4)	6.5 ± 1.2 (6.8) (n = 19)				-0.276
3	33	1.4 ± 0.4 (1.3)	6.8 ± 1.9 (6.5) (n = 21)				-0.077
4	38	1.4 ± 0.3 (1.3)	8.1 ± 2.1 (7.4) (n = 23)				0.220
5	44	1.4 ± 0.6 (1.3)	8.2 ± 2.0 (7.7) (n = 28)				0.043
6	50	1.4 ± 0.4 (1.4)	8.8 ± 3.3 (8.2) (n = 30)	97 ± 13	0.275	0.056	-0.434*
7	62	1.4 ± 0.4 (1.4)	9.0 ± 2.9 (8.9) (n = 43)	97 ± 12	-0.025	-0.180	-0.217
8	65	1.3 ± 0.4 (1.2)	9.6 ± 3.1 (9.4) (n = 41)	96 ± 12 (n = 64)	-0.164	-0.230	-0.421**
9	70	1.4 ± 0.5 (1.3)	9.8 ± 3.3 (9.1) (n = 47)	93 ± 12 (n = 69)	-0.054	-0.030	-0.506**
10	82	1.3 ± 0.4 (1.2)	10.3 ± 3.4 (10.5) (n = 50)	89 ± 12 (n = 81)	0.090	-0.203	-0.346*
11	81	1.3 ± 0.5 (1.3)	11.2 ± 3.3 (11.3) (n = 49)	87 ± 12 (n = 80)	-0.103	0.084	-0.304*
12	91	1.3 ± 0.5 (1.3)	11.0 ± 3.0 (11.1) (n = 68)	84 ± 13	0.047	-0.123	-0.317**
13	83	1.4 ± 0.5 (1.2)	10.5 ± 3.5 (10.4) (n = 55)	83 ± 14 (n = 81)	0.056	-0.259	-0.322*
14	67	1.4 ± 0.5 (1.2)	11.9 ± 4.1 (11.0) (n = 44)	80 ± 16 (n = 66)	-0.042	-0.361*	-0.086
15	76	1.4 ± 0.5 (1.4)	12.4 ± 4.3 (12.1) (n = 52)	76 ± 16	0.045	-0.526**	-0.136
16	64	1.5 ± 0.6 (1.4)	12.4 ± 3.6 (12.2) (n = 45)	79 ± 17	-0.027	-0.348*	-0.418**
17	63	1.5 ± 0.6 (1.4)	13.1 ± 3.2 (12.2) (n = 40)	79 ± 16 (n = 62)	-0.154	-0.342*	-0.034

** significant at 0.01 level * significant at 0.05 level

Supplemental Table 2a. Comparison of mean forced expiratory volume in 1 second expressed as % predicted per year of age set out against serum retinol levels, categorised at the <50th or >50th percentile of the US National Health and Nutrition Examination Survey (NHANES), derived from 846 measurements of 198 patients with cystic fibrosis.

Age	<50th percentile	>50th percentile	*P*
6	93 ± 14 (n = 25)	101 ± 10 (n = 25)	0.029
7	97 ± 11 (n = 27)	97 ± 13 (n = 35)	0.994
8	96 ± 12 (n = 39)	96 ± 12 (n = 25)	0.831
9	91 ± 13 (n = 41)	95 ± 12 (n = 28)	0.288
10	88 ± 11 (n = 46)	90 ± 14 (n = 35)	0.689
11	89 ± 12 (n = 55)	84 ± 12 (n = 25)	0.070
12	84 ± 13 (n = 72)	86 ± 14 (n = 19)	0.838
13	82 ± 15 (n = 59)	85 ± 12 (n = 22)	0.313
14	81 ± 17 (n = 53)	77 ± 12 (n = 13)	0.249
15	75 ± 18 (n = 54)	79 ± 10 (n = 22)	0.684
16	81 ± 17 (n = 41)	75 ± 15 (n = 23)	0.087
17	80 ± 17 (n = 35)	77 ± 16 (n = 27)	0.390

Supplemental Table 2b. Comparison of mean forced expiratory volume in 1 second expressed as % predicted per year of age set out against serum retinol levels, categorised into the <2.5th, 2.5th – 50th, 50th – 97.5th or the >97.5th percentile of the US National Health and Nutrition Examination Survey (NHANES), derived from 846 measurements of 198 patients with cystic fibrosis.

Age	<2.5th percentile	2.5th – 50th percentiles	50th – 97.5th percentiles	>97.5th percentile	*p*
6	62 (n = 1)	94 ± 12 (n = 24)	101 ± 10 (n = 22)	100 ± 7 (n = 3)	0.081
7	90 ± 16 (n = 4)	99 ± 10 (n = 23)	97 ± 14 (n = 30)	96 ± 5 (n = 5)	0.681
8	101 ± 10 (n = 5)	96 ± 12 (n = 34)	97 ± 12 (n = 22)	92 ± 12 (n = 3)	0.754
9	- (n = 0)	91 ± 13 (n = 41)	95 ± 17 (n = 21)	95 ± 17 (n = 7)	0.538
10	91 ± 9 (n = 10)	88 ± 12 (n = 36)	88 ± 13 (n = 31)	99 ± 15 (n = 4)	0.407
11	94 ± 12 (n = 12)	88 ± 12 (n = 43)	84 ± 12 (n = 23)	87 ± 15 (n = 2)	0.077
12	84 ± 14 (n = 26)	85 ± 12 (n = 46)	85 ± 13 (n = 17)	90 ± 29 (n = 2)	0.991
13	81 ± 15 (n = 23)	82 ± 14 (n = 36)	86 ± 12 (n = 19)	81 ± 9 (n = 3)	0.683
14	80 ± 19 (n = 16)	81 ± 16 (n = 37)	78 ± 13 (n = 11)	70 ± 1 (n = 2)	0.528
15	76 ± 17 (n = 15)	75 ± 19 (n = 39)	79 ± 10 (n = 20)	76 ± 16 (n = 2)	0.959
16	75 ± 20 (n = 16)	85 ± 14 (n = 25)	76 ± 16 (n = 21)	67 ± 13 (n = 2)	0.065
17	86 ± 19 (n = 11)	77 ± 16 (n = 24)	78 ± 16 (n = 26)	67 (n = 1)	0.228

Supplemental Table 3a. Comparison of mean forced expiratory volume in 1 second expressed as % predicted per year of age, set out against serum immunoglobulin G levels, categorised into the <50th or >50th percentile of the paediatric reference intervals for Caucasian children, derived from 564 measurements of 190 patients with cystic fibrosis.

Age	<50th percentile	>50th percentile	*P*
6	95 ± 12 (n = 21)	101 ± 15 (n = 9)	0.178
7	99 ± 13 (n = 26)	98 ± 10 (n = 17)	0.585
8	96 ± 13 (n = 22)	93 ± 12 (n = 19)	0.441
9	93 ± 15 (n = 26)	91 ± 12 (n = 21)	0.623
10	90 ± 13 (n = 22)	87 ± 13 (n = 28)	0.558
11	87 ± 8 (n = 15)	88 ± 13(n = 34)	0.208
12	87 ± 12 (n = 32)	82 ± 14 (n = 36)	0.201
13	84 ± 14 (n = 31)	83 ± 15 (n = 24)	0.966
14	85 ± 11 (n = 20)	80 ± 18 (n = 24)	0.187
15	82 ± 15 (n = 18)	67 ± 18 (n = 34)	0.014
16	84 ± 15 (n = 16)	77 ± 17 (n = 29)	0.420
17	85 ± 14 (n = 12)	78 ± 16 (n = 28)	0.224

Supplemental table 3b. Comparison of mean forced expiratory volume in 1 second expressed as % predicted per year of age, set out against serum immunoglobulin G levels, categorised into the <2.5th, 2.5th – 50th, 50th – 97.5th or the >97.5th percentile of the paediatric reference intervals for Caucasian children, derived from 564 measurements of 190 patients with cystic fibrosis.

Age	<2.5th percentile	2.5th – 50th percentiles	50th – 97.5th percentiles	>97.5th percentile	*p*
6	100 ± 10 (n = 5)	93 ± 12 (n = 16)	102 ± 13 (n = 7)	97 ± 26 (n = 2)	0.449
7	110 ± 10 (n = 7)	95 ± 12 (n = 19)	99 ± 10 (n = 16)	96 (n = 1)	0.086
8	98 ± 14 (n = 4)	96 ± 13 (n = 18)	93 ± 13 (n = 16)	92 ± 11 (n = 3)	0.832
9	85 ± 20 (n = 3)	94 ± 14 (n = 23)	91 ± 13 (n = 18)	87 ± 1 (n = 3)	0.504
10	101 ± 14 (n = 3)	88 ± 13 (n = 19)	87 ± 13 (n = 26)	82 ± 1 (n = 2)	0.319
11	- (n = 0)	84 ± 8 (n = 15)	88 ± 12 (n = 30)	91 ± 20 (n = 4)	0.441
12	84 ± 10 (n = 4)	87 ± 12 (n = 28)	83 ± 14 (n = 26)	81 ± 17 (n = 10)	0.591
13	91 ± 14 (n = 8)	82 ± 14 (n = 23)	88 ± 13 (n = 19)	67 ± 14 (n = 5)	0.035
14	78 ± 3 (n = 3)	87 ± 12 (n = 17)	84 ± 18 (n = 14)	73 ± 14 (n = 10)	0.136
15	86 ± 7 (n = 4)	81 ± 16 (n = 14)	72 ± 15 (n = 22)	63 ± 21 (n = 12)	0.043
16	89 (n = 1)	84 ± 15 (n = 15)	78 ± 17 (n = 17)	75 ± 18 (n = 12)	0.673
17	-- (n = 0)	85 ± 14 (n = 12)	82 ± 18 (n = 14)	74 ± 14 (n = 14)	0.132

7.3

Vitamin E intake, alpha-tocopherol levels and pulmonary function in children and adolescents with cystic fibrosis

(Abstract, statistics, results, discussion, conclusion)

British Journal of Nutrition. In press

Abstract

Aim

Pancreatic insufficient cystic fibrosis (CF) patients receive vitamin E supplementation according to CF-specific recommendations to prevent deficiencies. It has been suggested that higher serum α-tocopherol levels could have protective effects on pulmonary function (PF) in patients with CF. Whether current recommendations are indeed optimal for preventing deficiency and whether vitamin E has therapeutic benefits are subjects of debate.

Methods

We studied vitamin E intake, and the long-term effect of vitamin E intake, the coefficient of fat absorption (CFA) and immunoglobulin G (IgG) on α-tocopherol levels. We also examined the long-term effect of serum α-tocopherol and serum IgG on forced expiratory volume in 1 second expressed as % of predicted (FEV_1% pred.) in paediatric CF patients during a 7-year follow up period.

Results

We found that CF patients failed to meet the CF-specific vitamin E recommendations, but serum α-tocopherol below the 2.5^{th} percentile was found in only 23 out of the 1022 measurements (2%). Furthermore, no clear effect of vitamin E intake or CFA on serum α-tocopherol was found ($p \geq 0.103$). FEV_1% pred. was longitudinally inversely associated with age ($p < 0.001$) and serum IgG ($p = 0.003$), but not related to serum α-tocopherol levels.

Conclusion

In this large sample of children and adolescents with CF, vitamin E intake was lower than recommended, but serum α-tocopherol deficiency was rare. We found no evidence that higher serum α-tocopherol levels had protective effects on PF. Adjustment of the recommendations to the real-life intake of these patients may be considered.

Statistics

The total vitamin E intake was expressed as % of the lower level (LL) and the upper level (UL) of both the European and North-American CF-specific recommendations. To assess whether total vitamin E intake and PF were related to serum α-tocopherol levels, the children were categorised on the basis of their serum α-tocopherol as having a level at the $<50^{th}$ or $>50^{th}$ percentile, or a level between the 2.5^{th} and 97.5^{th} percentiles, and the $>97.5^{th}$ percentile of the US National Health and Nutrition Examination Survey (NHANES). The total vitamin E intake or FEV_1% pred. outcomes among the categories of serum α-tocopherol levels were compared, using the Mann-Whitney test. For longitudinal analyses, linear mixed-model regression was performed to evaluate the effect of total vitamin E intake, CFA, serum IgG, gender and age on serum α-tocopherol. Included were fixed effects for total vitamin E intake, the CFA, serum IgG, gender and age of child and a random intercept and random slope for age of child to account for correlations between measurements within children. In the linear mixed-model regression, serum α-tocopherol was log-transformed to correct for right-skewness. We also examined the longitudinal effect of serum α-tocopherol and serum IgG on PF: in this model fixed effects for serum α-tocopherol, serum IgG, age of child, and gender, and a random intercept and random slopes for serum α-tocopherol and age of child, were included.

Results

Clinical characteristics

A total of 232 patients with proven CF (97% Caucasian, 112 girls) were eligible for inclusion. In these patients, we obtained a total of 912 measurements of vitamin E intake, and 1,022, 672, 679 and 874 measurements, respectively, of serum α-tocopherol, CFA, serum IgG, and FEV_1% pred.

Vitamin E intake

The mean total vitamin E intake (dietary vitamin E intake plus prescribed supplementation) of 218 patients in the different age groups was between 55 mg and 150 mg α-tocopherol per day. A gradual increase was seen with age. The vitamin E intake was higher from supplements than from dietary sources (Figure 1, Table 1). The European and North-American lower level of the CF-specific vitamin E supplementation recommendations[1, 2] were only met in adolescents 15 years and older and in children less than 1 year of age. In all age groups, the prescribed supplementation was far below the upper limits of both the European, and the North-American recommendations (Table 1).

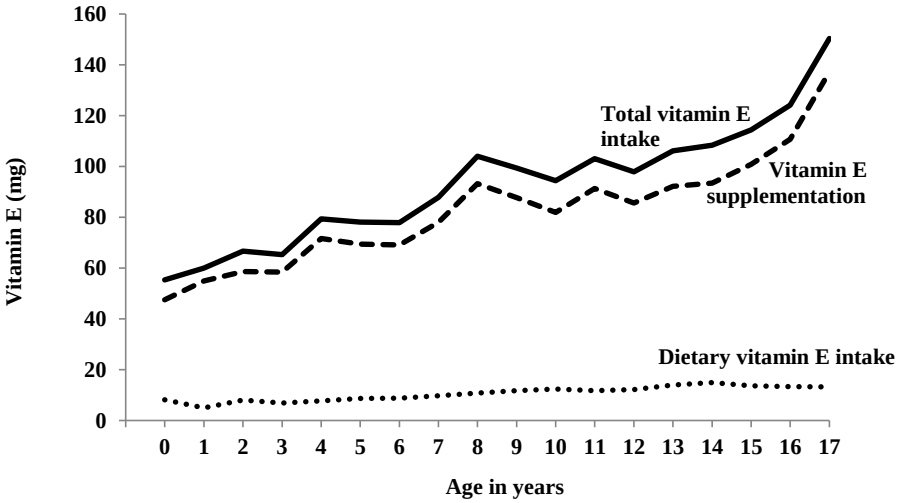

Figure 1. Mean dietary vitamin E intake, prescribed supplementation and total vitamin E intake (dietary vitamin E intake plus prescribed supplementation), expressed as mg α-tocopherol per year of age, derived from 912 dietary measurements of 218 patients with CF.

Clinical measurements

The median serum α-tocopherol levels varied between 775 µg/dL and 1,079 µg/dL and were all above the 50th percentile of the NHANES (Figure 2). In children aged 6 years and older, in 23 measurements (2%) a serum α-tocopherol level at the <2.5th percentile was found, and in 122 measurements (12%) a level at the >97.5th percentile. The median CFA varied between 89% and 94%. Serum IgG, with medians between 3.9 g/L and 12.4 g/L, gradually increased whereas FEV_1% pred. gradually declined with age (Supplemental Table 1).

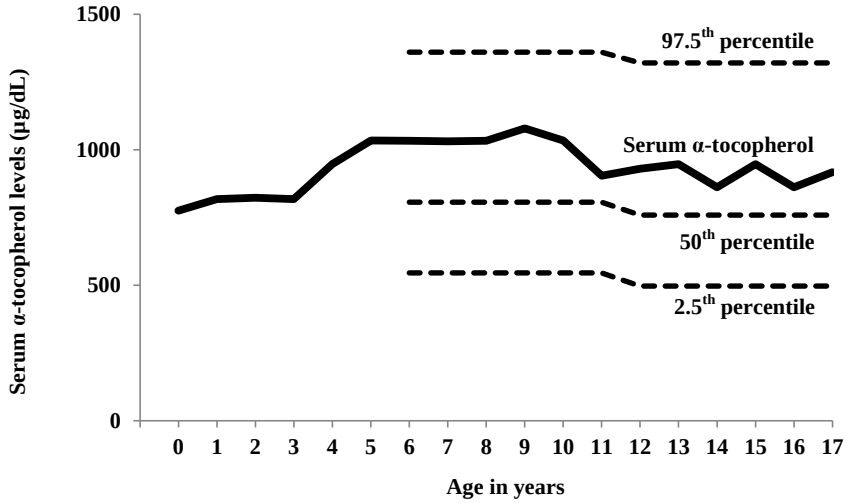

Figure 2. Median serum α-tocopherol, expressed as microgramme/decilitre (µg/dL) per year of age, derived from 1,022 measurements of 229 patients with cystic fibrosis set out against the US National Health and Nutrition Examination Survey (NHANES) reference percentiles (dotted lines).

Serum α-tocopherol levels and PF

To assess whether better PF were related to higher serum α-tocopherol levels, the mean FEV_1% pred. outcomes among the serum α-tocopherol categories, as having a level at the $<50^{th}$ or $>50^{th}$ percentile of the NHANES, for each year of age were examined. We found a difference in the distribution of FEV_1% pred. across the serum α-tocopherol categories for patients in age groups 8 ($p=0.016$), 11 ($p=0.028$) and 12 ($p=0.004$), with a lower FEV_1% pred. in the patients with a serum α-tocopherol at the $>50^{th}$ percentile. In addition, an overall trend towards a lower FEV_1% pred. in those with a serum α-tocopherol level at the $>50^{th}$ percentile was seen (Figure 3, see also Supplemental Table 2 for detailed information). The distribution of FEV_1% pred. across serum α-tocopherol categories with levels between the 2.5^{th} and 97.5^{th} percentiles, and the $>97.5^{th}$ percentile did not differ (all $p\geq0.102$) (data not shown).

Table 1. Vitamin E intake (dietary intake, prescribed supplementation and total intake) derived from 912 measurements in 218 patients with cystic fibrosis (CF) expressed as mg α-tocopherol (mean ± standard deviation). The prescribed supplementation is also expressed as % of both the lower limit (LL) and upper limit (UL) of the European (EU) and North-American (US) CF-specific vitamin E recommendations.

Age	N	CF recommendation supplementation				Dietary intake	Supplementation
		EU LL	EU UL	US LL	US UL		
0	6	100	400	40	50	8.1 ± 1.5	47.5 ± 5.6
1	18	100	400	80	150	5.0 ± 2.5	54.9 ± 16.7
2	22	100	400	80	150	8.0 ± 4.9	58.6 ± 24.6
3	36	100	400	80	150	6.9 ± 4.0	58.4 ± 28.9
4	35	100	400	100	200	7.7 ± 3.7	71.6 ± 41.6
5	46	100	400	100	200	8.7 ± 4.8	69.4 ± 38.8
6	50	100	400	100	200	8.8 ± 5.7	69.1 ± 39.0
7	56	100	400	100	200	9.7 ± 5.5	78.0 ± 52.5
8	63	100	400	100	200	10.8 ± 6.4	93.2 ± 84.6
9	73	100	400	200	400	11.7 ± 7.4	87.7 ± 75.9
10	76	100	400	200	400	12.4 ± 6.9	81.9 ± 58.4
11	81	100	400	200	400	11.7 ± 6.1	91.3 ± 77.7
12	78	100	400	200	400	12.2 ± 7.5	85.6 ± 63.5
13	72	100	400	200	400	14.0 ± 7.0	92.2 ± 66.9
14	64	100	400	200	400	14.9 ± 8.4	93.4 ± 65.8
15	50	100	400	200	400	13.6 ± 7.9	100.8 ± 89.1
16	52	100	400	200	400	13.3 ± 6.2	110.7 ± 97.7
17	34	100	400	200	400	13.2 ± 9.2	137.2 ± 111.6

Table 1. Continued.

Age	N	Total intake	Prescribed supplementation as % of CF- recommendations			
			EU LL	EU UL	US LL	US UL
0	6	55.3 ± 6.6	48 ± 6	12 ± 1	119 ± 14	95 ± 11
1	18	60.0 ± 16.2	55 ± 17	14 ± 4	69 ± 21	37 ± 11
2	22	66.7 ± 25.3	59 ± 25	15 ± 6	73 ± 31	39 ± 16
3	36	65.3 ± 28.3	58 ± 29	15 ± 7	73 ± 36	39 ± 19
4	35	79.3 ± 41.4	72 ± 42	18 ± 10	72 ± 42	36 ± 21
5	46	78.1 ± 39.1	69 ± 39	17 ± 10	69 ± 39	35 ± 19
6	50	77.9 ± 38.4	69 ± 39	17 ± 10	69 ± 39	35 ± 19
7	56	87.8 ± 52.2	78 ± 53	20 ± 13	78 ± 53	39 ± 26
8	63	104.0 ± 85.2	93 ± 85	23 ± 21	93 ± 85	47 ± 42
9	73	99.3 ± 77.9	88 ± 76	22 ± 19	45 ± 42	22 ± 19
10	76	94.4 ± 59.2	82 ± 58	20 ± 15	41 ± 29	20 ± 15
11	81	103.0 ± 78.0	91 ± 78	23 ± 19	46 ± 39	23 ± 19
12	78	97.9 ± 63.2	86 ± 64	21 ± 16	43 ± 32	21 ± 16
13	72	106.1 ± 67.6	92 ± 67	23 ± 17	46 ± 33	23 ± 17
14	64	108.3 ± 64.7	93 ± 66	23 ± 16	47 ± 33	23 ± 16
15	50	114.4 ± 89.1	101 ± 89	25 ± 22	50 ± 45	25 ± 22
16	52	124.1 ± 96.6	111 ± 98	28 ± 24	55 ± 49	28 ± 24
17	34	150.3 ± 111.2	137 ± 112	34 ± 28	69 ± 56	34 ± 28

Additionally, with the linear mixed-model analysis, we observed no significant relation between FEV_1% pred. and serum α-tocopherol levels (95% CI -0.00% to 0.00%, p=0.158), but FEV_1% pred. was associated with age and serum IgG. Each year increase in age was associated with a 1.84% (95% CI -2.22% to -1.45%, p<0.001) decline in FEV_1% pred. and each g/L increase in serum IgG was associated with a 0.53% (95% CI -0.89% to -0.18%, p=0.003) decline in FEV_1% pred.

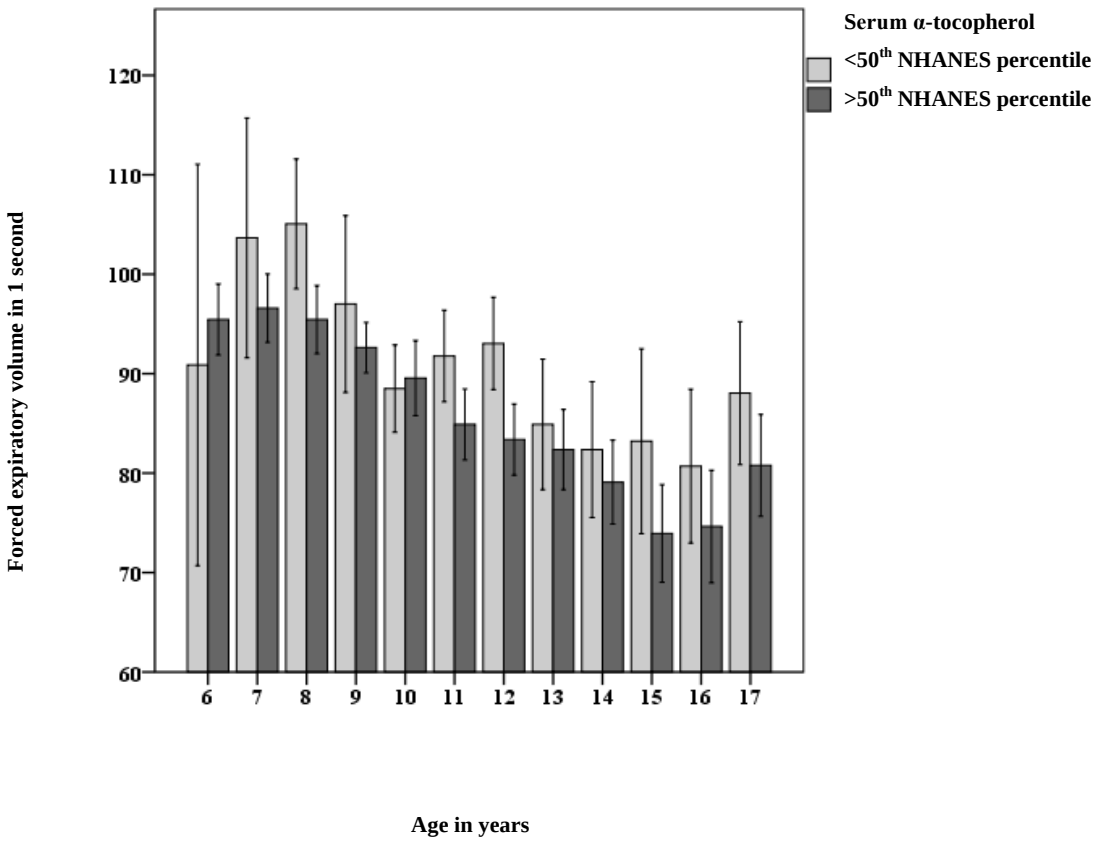

Figure 3. Mean forced expiratory volume in 1 second expressed as percentage of predicted (FEV_1% predicted, ± 1 SD) per year of age, categorised for serum α-tocopherol levels at the <50th or >50th percentile (according to the normal reference range of the US National Health and Nutrition Examination Survey (NHANES)) derived from 783 measurements of 194 patients with cystic fibrosis.

Discussion

The current study in this large sample of children and adolescents with CF, showed that both the European and the North-American CF-specific recommendations for vitamin E intake were not met, but serum α-tocopherol deficiency was rare. Longitudinally, no associations of total vitamin E intake, CFA and serum IgG with serum α-tocopherol were found. Also no correlation between serum α-tocopherol and FEV_1% pred. was observed, but decreasing FEV_1% pred. was associated with increasing age and serum IgG.

A North-American cross-sectional study of vitamin E status in 69 subjects with CF, aged 7 – 10 years, reported a mean dietary vitamin E intake of 6 mg/day, and a median CFA of 87%[3] which are both slightly below our findings (daily dietary vitamin E intake between 9 mg and 12 mg, median CFA between 91% and 92%). The total vitamin E intake (dietary intake plus supplementation) in this North-American study was in accordance with the North-American CF-specific recommendation, and much higher than we found (a total intake of 224 mg versus 88 mg – 104 mg in our group, aged 7 – 10 years). Nevertheless, neither they nor we found an association between serum α-tocopherol and vitamin E intake or between serum α-tocopherol and CFA. Also serum α-tocopherol levels in their study were in the same range as we found: respectively 1,131 µg/dL versus levels between 1,031 µg/dL and 1,079 µg/dL for these 7 – 10 year old children.

In our study sample, the current CF-specific recommendations for vitamin E supplementation were not met; nevertheless, median serum α-tocopherol levels were normal in all age groups. The vitamin E intake achieved in our cohort seems to be sufficient to maintain a normal serum α-tocopherol level despite a supplementation only at 50% of the current recommendations. This suggests that both the European and North-American CF-specific recommendations for vitamin E supplementation are higher than necessary to prevent deficiencies, and may even lead to supranormal levels, as were found in 12% of our cohort. In this respect it is noteworthy that vitamin E supplementation above 400 IU/day, the current upper recommended level in CF patients, may result in toxic effects, e.g. an increased risk of death in adults [4], and an increased risk of haemorrhagic stroke .[5] Although vitamin E toxicity in children has not been described, the former studies may raise questions about the safety of the high levels of vitamin E supplementation recommendations for children and adolescents with CF.

We found no association between the CFA and serum α-tocopherol which is in line with a study in CF patients in whom identical serum α-tocopherol levels were found in both pancreatic sufficient and pancreatic insufficient patients.[6] In the current study sample near-normal CFA outcomes were encountered, although a lesser proportion of patients completed fat-balance studies with increasing age. The available CFA outcomes suggested that in current practice fat malabsorption is usually well-treated, reducing the loss of fat-soluble vitamins and making a potential effect of fat malabsorption on serum α-tocopherol hard to detect, at least in those with completed fat-balance studies.

The preventive use of a high dosage vitamin E as an anti-oxidant is a subject of debate, as contradictory, but generally disappointing, findings have been reported.[7] In vivo, it has been shown that serum α-tocopherol have no protective function against oxidative damage.[8] This is supported by our results and those of previous studies[3, 9], since no evidence was obtained that higher serum α-tocopherol levels have a protective effect on PF in patients with CF. However, a French longitudinal study, including 312 paediatric and adult patients with CF, reported a positive correlation between FEV_1% pred. and higher serum α-tocopherol levels.[10] The age range in that study differed from our study: 1 – 45 years of age[10] versus 0 – 18 years of age in our cohort, although serum α-tocopherol levels were in the same range as we found: 21 µmol/L (≈ 908 µg/dL) versus levels between 755 and 1,079 µg/dL. Associations between low serum α-tocopherol and compromised PF may be present in adults, who generally have a more severely reduced FEV_1% pred. than children, as a result of the prolonged nature of the disease. As only a few patients in our study had a severely decreased PF, we could not reliably assess a potentially protective effect of serum α-tocopherol when FEV_1% pred. is already severely compromised. Nevertheless, within the serum α-tocopherol distribution as seen in our cohort, with almost all patients having levels within, or in 12% of the measurements, even above the normal NHANES reference ranges, we found the opposite: a trend towards higher serum α-tocopherol levels in patients with lower PF. This once again casts doubt on the hypothesis that vitamin E boosts antioxidant defences and thus offset oxidant damage, at least in the age range of our study sample.

It has been proposed that the serum α-tocopherol/total lipid ratio is a more correct index of vitamin E status than serum α-tocopherol measurements alone.[11] Nevertheless, studies using both the ratio of plasma vitamin E to total plasma lipids and the serum α-tocopherol level to detect patients with a vitamin E deficiency only find minor differences between both methods[12-14], while it is unclear which method is superior. Consequently there is no consensus for reporting the vitamin E status in CF patients.[15] In this study sample, we were interested in examining serum α-tocopherol levels, which were clinically available and which could be compared with reference values obtained in healthy counterparts of the same age.

Because this was a single centre study, the results might not be generalizable to other CF treatment centres and populations. Moreover, keeping food records can be burdensome, leading to alterations of the diet and to over- and/or under-reporting, which affects the validity. Lastly, patient adherence to vitamin supplementation might be a problem, which

would lead to overestimation of the true total vitamin E intake in the present study and may have prevented us from observing a correlation between total vitamin E intake and serum α-tocopherol levels.

Conclusion

In this large sample of children and adolescents with CF, the current international recommendations for vitamin E supplementation in CF were not met. Nevertheless, median serum α-tocopherol levels were within reference values. We found no evidence that higher serum α-tocopherol levels had protective effects on PF. An adjustment of the recommendations to the real-life intake in these patients may be considered.

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Supplemental Table 1. Serum α-tocopherol, coefficient of fat absorption (CFA), serum immunoglobulin G (IgG) and forced expiratory volume in 1 second expressed as percentage of predicted (FEV_1% pred.), derived from 1,126 measurements of 232 patients with cystic fibrosis.

Age	N (♀)	Serum α-tocopherol (µg/dL) *	CFA (%) *	Serum IgG (g/L) *	FEV_1% pred. **
0	17 (9)	775 (660 – 1,066) (n = 16)	-	3.9 (3.2 – 6.1) (n = 5)	
1	32 (16)	818 (689 – 1,034) (n = 31)	89 (n = 1)	5.7 (4.8 – 6.5) (n = 10)	
2	27 (15)	823 (689 – 1,033) (n = 24)	92 (78 – 94) (n = 4)	6.6 (5.1 – 7.5) (n = 17)	
3	41 (25)	818 (689 – 947) (n = 39)	91 (85 – 96) (n = 18)	6.7 (5.4 – 7.4) (n = 26)	
4	41 (21)	947 (775 – 1,227) (n = 38)	90 (85 – 93) (n = 29)	7.2 (6.3 – 9.6) (n = 23)	
5	48 (23)	1,034 (861 – 1,163) (n = 47)	92 (88 – 96) (n = 35)	7.5 (6.4 – 9.7) (n = 30)	
6	60 (30)	1,033 (904 – 1,249) (n = 55)	90 (86 – 94) (n = 43)	7.8 (6.1 – 9.9 (n = 34)	96 ± 13 (n = 53)
7	66 (32)	1,031 (904 – 1,206) (n = 58)	92 (85 – 96) (n = 46)	8.1 (6.8 – 11.5) (n = 43)	96 ± 12 (n = 62)
8	69 (31)	1,033 (818 – 1,249) (n = 62)	92 (89 – 95) (n = 55)	8.1 (6.4 – 11.4) (n = 35)	98 ± 12 (n = 66)
9	84 (43)	1,079 (904 – 1,249) (n = 80)	91 (87 – 95) (n = 60)	9.2 (7.5 – 11.5) (n = 52)	94 ± 11 (n = 80)
10	84 (40)	1,034 (812 – 1,335) (n = 78)	92 (88 – 95) (n = 68)	10.4 (7.7 – 12.4) (n = 54)	89 ± 13 (n = 82)
11	95 (50)	904 (721– 1,137) (n = 82)	92 (88 – 95) (n = 62)	11.2 (8.3 – 12.1) (n = 48)	87 ± 12 (n = 90)
12	93 (48)	930 (732 – 1,163) (n = 81)	91 (87 – 95) (n = 60)	11.1 (8.3 – 13.0) (n = 65)	86 ± 13 (n = 91)
13	88 (46)	947 (754 – 1,120) (n = 77)	94 (89 – 96) (n = 59)	10.4 (8.1 – 12.3) (n = 61)	82 ± 14 (n = 84)
14	81 (41)	861 (732 – 1,034) (n = 72)	92 (89 – 96) (n = 45)	11.5 (9.5 – 15.0) (n = 50)	80 ± 15 (n = 78)
15	72 (34)	947 (775 – 1,120) (n = 64)	92 (90 – 95) (n = 36)	12.1 (9.0 – 15.2) (n = 41)	76 ± 16 (n = 66)
16	73 (33)	861 (689 – 1,249) (n = 67)	90 (84 – 93) (n = 36)	12.4 (10.0 – 16.1) (n = 49)	77 ± 18 (n = 71)
17	55 (24)	917 (689 – 1,249) (n = 51)	89 (83 – 94) (n = 15)	12.1 (10.2 – 15.4) (n = 36)	82 ± 14 (n = 51)

* median (25^{th} – 75^{th} percentiles) ** mean ± SD

Supplemental Table 2: Comparison of mean forced expiratory volume in 1 second expressed as percentage of predicted per year of age set out against serum α-tocopherol, categorised for serum α-tocopherol levels at the <50th or >50th percentile (according to the normal reference range of the US National Health and Nutrition Examination Survey (NHANES)) derived from 783 measurements of 194 patients with cystic fibrosis.

Age	<50th percentile	>50th percentile	*p*
6	91 ± 19 (n = 6)	95 ± 11 (n = 42)	0.616
7	104 ± 11 (n = 6)	97 ± 12 (n = 48)	0.273
8	105 ± 11 (n = 13)	95 ± 12 (n = 46)	0.016
9	97 ± 14 (n = 12)	93 ± 10 (n = 64)	0.251
10	89 ± 8 (n = 17)	90 ± 14 (n = 59)	0.489
11	92 ± 12 (n = 28)	85 ± 13 (n = 50)	0.028
12	93 ± 10 (n = 22)	83 ± 13 (n = 57)	0.004
13	85 ± 13 (n = 18)	82 ± 15 (n = 55)	0.569
14	82 ± 17 (n = 26)	79 ± 14 (n = 43)	0.556
15	83 ± 15 (n = 12)	74 ± 17 (n = 46)	0.074
16	81 ± 19 (n = 25)	75 ± 16 (n = 40)	0.112
17	88 ± 12 (n = 14)	81 ± 15 (n = 34)	0.066

8

Summarizing discussion and future directions

Summarizing discussion and future directions

In cystic fibrosis, lung disease and nutritional status are tightly intertwined. Malnutrition, as a result of energy losses due to malabsorption, inadequate caloric intake and increased energy metabolism, is associated with poor clinical outcomes.[1,2] Therefore, regular evaluation of nutritional status is an integral part of CF-care. CF-specific guidelines give recommendations for the monitoring of nutritional intake and growth, strategies to prevent malnutrition and interventions in patients with nutritional failure, as well as for the control of intestinal fat malabsorption.[3,4]

Part 1: Dietary intake in children and adolescents with cystic fibrosis

Patients suffering from weight loss or malnutrition must optimise their dietary intake, and if this turns out to be unsuccessful for improving the nutritional status, invasive nutritional intervention should be started.[3,4] However, no advice on the type of intervention, such as enteral tube feeding, oral supplementation or behavioural intervention, was available. We therefore performed a systematic review of the effectiveness of nutritional interventions in patients with CF, with weight gain as the primary outcome (Chapter 2). We found that interventions using enteral tube feeding have so far only been studied in patients with weight index z-scores below -1, oral supplementation has only been studied in patients with z-scores below 0 but above -2, and behavioural intervention studies have only been conducted in those with z-scores above -1. Despite the heterogeneity in the cohorts studied with respect to nutritional status, some general conclusions could be drawn. Enteral tube feeding seems especially successful in clearly malnourished patients, as it improved the nutritional status and slowed the decline in pulmonary function. In patients with weight indexes z-scores below 0 and above -2, the addition of oral supplementation seems successful in improving weight and/or increasing total caloric intake. To date, the results of behavioural interventions are unclear. Overall, no positive effects of behavioural interventions or oral supplementation on pulmonary function have been described (Chapter 2). Future studies might determine more precisely which patient group may benefit most from behavioural interventions and/or oral supplements with respect to nutritional status and pulmonary function.

Adequate energy intake to achieve optimal growth in patients with CF has contributed to the increased survival achieved in the last several decades,[2] and therefore the CF-specific guidelines recommend a high-caloric[4,5] and high-fat diet.[3] However, in clinical practise,

children and adolescents with CF have a caloric intake that is below, or in the lower range of the recommended 110% – 200% of the gender- and age-specific estimated average requirements (EAR),[6-8] actually varying between 88% and 127% of the EAR (Chapter 3). Nevertheless, their absolute caloric intake was significantly higher than in the controls[6,8] (Chapter 3). The recommendations for high caloric intake may have negative consequences, as overweight and obesity in the paediatric CF patient population is becoming a concern, with a prevalence of 10% – 23%.[9,10] Moreover, there was no benefit to continuing to increase weight above the normal range in paediatric CF patients, in terms of survival and pulmonary function.[9] The same was true for the adult population: the profits of increasing weight for pulmonary function are blunted above a BMI of 23 – 25 kg/m^2.[10,11] Therefore, it seems unnecessary to continue a high-caloric diet once weight is above average.

The use of the EAR in CF-specific guidelines has additional limitations. The EAR, based on resting energy expenditure, physical activity level and deposit energy for growth, has been developed to cover a level of caloric intake that meets the requirement of half of the healthy population in age groups often comprising 3 – 5 years. The use of such large age groups has limitations: when a child reaches the first year of the next age group, he or she has to meet a significantly higher caloric intake overnight to achieve the EAR. This is demonstrated by the steep slope in caloric intake expressed as EAR between age groups, and the gradual increase in the actual caloric intake within the age group (Chapter 3). It is also well-known that energy demands alter during successive years as a result of the ever-changing energy needs for growth. Therefore, recommendations for EAR in childhood should be confined to a 1-year age interval. We also found that in healthy controls, the current EAR was only met in early childhood, while an intake below the EAR was found in the older age groups (Chapter 3), raising questions about whether these EAR recommendations are still up-to-date. Moreover, a wide variability in caloric intake, expressed as %EAR, was calculated within the different EAR age groups (Chapter 3). Given the discrepancy between the EAR and the actual caloric intake of healthy controls, the latter, rather than the EAR, should be the reference when evaluating the caloric intake in CF patients with normal weight- and height-growth and near-normal or normal pulmonary function. In these patients, an intake slightly above the intake of their healthy counterparts, 4% to 11%,[12-14] should be pursued since they have a mildly increased normal caloric need compared to the healthy counterparts.[12-19] Patients with growth retardation require a more tailored recommendation based on the child's individual needs, in which a comprehensive nutritional assessment, including data on energy expenditure and

physical activity level, could be used. For this purpose, predictive equations are available, based on measurements of energy expenditure in large reference populations. However, caution is necessary when applying these data to individuals in whom weight and height deviate from the pattern of the reference population, as estimates are based on energy 'need' instead of energy 'use'. Indeed, in individuals with CF, predictive equations have been shown to have limited application,[20-22] as outcomes resulted in an underestimation of the actual energy requirements of patients with CF.[21,22] An assessment, rather than a prediction, of energy expenditure[23,24] therefore seems to be more appropriate.
Children and adolescents with CF have a significantly higher intake of fat and saturated fat than their healthy counterparts. An excessive consumption of saturated fat has been found, accounting for 12% – 14% of the total energy intake (Chapter 3), which was well above the advised limit of 10 En%.[25] As survival still improves dramatically, previously unrecognised complications associated with excessive saturated fat intake, such as cardiovascular disease, may arise. Indeed, in adult CF patients, higher concentrations of total and LDL cholesterol were found.[11,26] Even in paediatric patients, arterial stiffness, a sign of premature atherosclerosis that causes increased risk of cardiovascular disease later in life, was already manifest during childhood.[27] This might be attributed to the systemic inflammatory state in CF patients,[27] but a contribution by the large amounts of dietary saturated fat intake, causing an increase in total and LDL cholesterol, cannot be excluded.[28] Therefore, partly replacing dietary saturated fat with polyunsaturated fat seems prudent, as this will cause a decrease in total and LDL cholesterol.[29]

Excessive fat malabsorption, up to 50% – 80% of the fat ingested, is seen in untreated pancreatic insufficient patients with CF. Pancreatic enzyme replacement therapy (PERT) is the proven therapy to substantially reduce this malabsorption. Appropriate PERT generally results in a CFA of more than 85%, and in many patients it is above 90%[30] (Chapter 4). Nevertheless, we found CFA outcomes below 85% in over 20% of the measurements, although most of these patients obtained a CFA above 85% in subsequent years (Chapter 4). Only those with a CFA that was consistently below 85% had a body-weight below the group average (Chapter 4).

Pancreatic enzyme dosages are based on lipase units per gram of fat ingested or on the patients' body weight, with an upper limit of 10,000 lipase units/kg/day.[3,4] It is unlikely that increasing PERT beyond this threshold will produce any benefit with respect to either fat

malabsorption[31,32] or growth.[33] This is supported by a study in which children who initially received more than 11,000 lipase units/kg/day reduced their PERT dosage to less than 10,000 lipase units/kg/day, but still had CFA outcomes of 92%, while growth parameters even improved.[34] Nevertheless, the optimal PERT dosage below 10,000 lipase units/kg/day remains unknown[33,35] (Chapter 4). In daily practice, the PERT dosage is therefore determined individually, as there is enormous variability in the response to PERT among patients, with no clear correlation between the CFA and PERT[36-38] (Chapter 4).

Besides PERT, other factors affecting the gastrointestinal tract[39-42] (e.g. persistent low intraluminal pH, slow transit, abnormal bile acid metabolism) or lack of adherence[7,32] might influence the CFA. Therapies other than PERT, such as laxative treatment[43,44] and/or proton pump inhibitors,[3] might be beneficial in improving the CFA, at least in those with constipation and/or low duodenal pH.

Due to the large therapeutic burden regarding drug treatment in patients with CF, it is important to use the minimum dose necessary to achieve acceptable control of intestinal malabsorption. In those with documented persistent malabsorption, further investigation on either adherence or coexisting disorders is recommended.

Part 2: Body-growth in children and adolescents with cystic fibrosis

Nutritional status and lung disease are closely intertwined; a suboptimal nutritional status is associated with an accelerated decline in pulmonary function.[1,45-49] The importance of regular evaluation of nutritional status is therefore evident. To this end, CF-specific guidelines include recommendations on monitoring nutritional status, including weight and height measurements.[3,4] However, caution is needed when applying weight and height measurements to identify patients at risk for nutritional failure, as these parameters may under- or overestimate the nutritional status.

Weight measurements do not give a good indication of body-tissue composition and do not reflect whether an excess or deficiency of weight is due to an increase or loss in fat mass, fat-free mass, or both. This is important because apparent or hidden fat-free mass depletion, rather than low body-weight,[50] is associated with a decline in pulmonary function.[50-54] Also, apparently well-nourished children and adolescents with CF who had depletion of fat-free mass[50-52,55-57] had reduced pulmonary function.[52,57,58] Likewise, the association between

weight gain and pulmonary function[46,48,59] (Chapter 5) is mediated through lean body mass rather than fat mass. Therefore, regular evaluation of body composition, reflecting changes due to growth, illness or nutritional rehabilitation, is necessary. Moreover, body-weight in proportion to attained height-growth may particularly underestimate the nutritional status. For example, normal z-scores for weight-for-height or body-mass-index were found in children with short stature and normal weight[60,61] and in those with a concomitant delay in both weight- and height-growth.[56] Moreover, catch-up growth might be easier to attain for weight. In our cohort study, we found a persistent delay in height-growth, while an increase in z-score for weight-for-height during the 8-year follow-up was seen (Chapter 5).

Height measurements do not adjust for genetic potential, i.e. target height, which results in an underestimated prevalence of short stature in children with tall parents and an overestimated prevalence in those with short parents[62] (Chapter 6). In order to avoid misclassification of nutritional status, height adjusted for genetic components should be included as a routine component of nutritional status assessment in all paediatric CF patients. Furthermore, height measurements do not take the child's skeletal maturation into account and CF is associated with a delayed bone-age,[63-65] to which both disease severity and nutritional status contribute.[65] We found delayed skeletal maturation in over 60% of our patients with a mean delay of 2.7 months, and in almost 20% with a delay of more than 1 year (Chapter 6). Therefore, in patients with delayed height-growth after adjustment for genetic potential, evaluation of bone age is advised in order to avoid misclassification of delayed height-growth.

<u>Part 3: Vitamin A and vitamin E intake in children and adolescents with cystic fibrosis</u>

In CF-care, the historical focus has been on preventing vitamin A and E deficiency, which is associated with the fat malabsorption found in pancreatic insufficient patients. Therefore, the CF-specific guidelines recommend a routine daily prescription of vitamin A and E for all pancreatic insufficient patients.[3,4] At present, severe fat malabsorption has become very rare (Chapter 4) and it is debatable whether these recommendations are still optimal or even too high. This is especially clear for vitamin A, as intakes well above the tolerable upper limit for healthy referents were found in CF patients[66-68] (Chapter 7.1), with concomitant supranormal serum retinol levels in more than 50%.[66,67] Excess vitamin A intake can be detrimental since it is primarily stored in the liver and is potentially toxic, which can be particularly harmful for those with CF-associated liver disease.[69,70] To our knowledge, no vitamin E toxicity in children has been described, although the safety of high levels of vitamin E supplementation

is questionable, since intakes at supranutritional levels resulted in increased mortality in adults.[71-74]

It has been suggested that higher serum retinol[75-78] and α-tocopherol levels[76,77] have protective effects on pulmonary function. Nevertheless, we and others failed to demonstrate any significant beneficial effect[68,79-82] (Chapter 7.2, 7.3). In those with higher serum α-tocopherol levels, we even found a trend towards lower pulmonary function (Chapter 7.3), suggesting adverse, rather than beneficial, effects of high α-tocopherol levels.

Serum retinol is also an acute-phase reactant and its levels are depressed during an inflammatory exacerbation, with recovery afterwards.[76,77,79,83] Chronic inflammation thus interferes with the correct assessment of serum retinol (Chapter 7.1, 7.2). Therefore, it is imperative to distinguish between low(er) levels due to inadequate nutritional intake and low(er) levels due to the inflammatory response, to prevent unnecessarily high vitamin A supplementation.

We and others demonstrated that with typical supplementation, although only at 50% of vitamin A and E recommendations, appropriate serum levels were within reference values[68] (Chapter 7.1, 7.3). This suggests that when patients comply with the current recommendations, they get more vitamin A[66-68] (Chapter 7.1) and E (Chapter 7.3) than necessary. Given these results and the large therapeutic burden of patients with CF, vitamin dosages around 50% of the recommendations could initially be used, with every-6-month evaluation of serum levels. When the levels are stable and within reference values, annual blood evaluation will be sufficient.

Conclusion

The outlook for patients with CF has dramatically improved over the past several years. As survival continues to increase, CF-care guidelines should evolve accordingly. Children and adolescents with CF had a caloric intake below recommended, although significantly higher than healthy controls. In this respect, it now seems to be more prudent to advise a caloric intake slightly above the age-specific intake, with individual adjustments for patients with deviant weight- and height-growth. Moreover, a reduction in saturated fat intake seems appropriate to avoid an increased risk for cardiovascular disease later in life. The pancreatic

enzyme replacement therapy has to be determined individually, as there is an enormous variability in the response to the therapy among patients, with no clear correlation between the coefficient of fat absorption and pancreatic enzyme dosages.
In order to prevent under- or overestimation of the nutritional status, a nutritional status assessment, including weight and height measurements, should be complemented with routine evaluation of body composition and with height measurements adjusted for genetic components and in those with a delayed height-growth, evaluation of the bone age is advised. Lastly, vitamin A and E supplementation at half the recommended dosages resulted in appropriate serum levels; therefore, dosages of 50% of the recommendations could be used, at least initially.

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9

Samenvatting

Voedselinname en lichaamsgroei bij cystic fibrosis

Hoofdstuk 1: Introductie

Cystic fibrosis (CF) is een erfelijke ziekte, waarbij verschillende klieren in het lichaam, zoals de longen, alvleesklier en lever, abnormaal taai slijm afscheiden. CF wordt gekenmerkt door een langzame progressieve achteruitgang van de longfunctie als gevolg van chronische luchtweginfecties. Patiënten met CF hebben vaak een exocriene pancreas insufficiëntie, waardoor vetten uit de voeding onvoldoende worden afgebroken en opgenomen door het lichaam. Dit kan onder meer leiden tot vetmalabsorptie, verliezen van vetoplosbare vitamines zoals vitamine A en vitamine E en ondervoeding. Longinfecties en de voedingsstatus zijn nauw met elkaar verbonden en beide zijn van invloed op de levensverwachting van patiënten met CF.

Deel 1: Voedselinname van kinderen en adolescenten met cystic fibrosis

Hoofdstuk 2: Voedingsinterventies bij patiënten met cystic fibrosis; een overzicht van de literatuur

Patiënten met CF met gewichtsverlies en/of ondervoeding krijgen het advies om een energieverrijkt dieet te volgen. Als dit niet leidt tot een verbetering van de voedingstoestand, wordt een voedingsinterventie geadviseerd. Het is echter onduidelijk wanneer welk type interventie: gedragsinterventie, orale supplementen of sondevoeding het meest effectief is. Dit proefschrift geeft een overzicht van de literatuur, waarin de effectiviteit van verschillende voedingsinterventies bij patiënten met CF, met als primaire uitkomst gewichtstoename, is beschreven.

Sondevoeding werd uitsluitend voorgeschreven aan patiënten met een gewicht van tenminste 1 standaarddeviatie-score onder het gemiddelde, voedingssupplementen aan patiënten met een gewicht tussen -2 en 0 standaarddeviatie-score, terwijl gedragsinterventies enkel werden toegepast bij patiënten met een gewicht boven -1 standaarddeviatie-score. Ondervoede patiënten die sondevoeding kregen toegediend, lieten een verbetering van de voedingstoestand zien en tevens een minder snelle achteruitgang van de longfunctie. Patiënten met een standaarddeviatie-score voor gewicht tussen -2 en 0 die voedingssupplementen kregen voorgeschreven, toonden een gewichtsvermeerdering en/of verhoogde energie-inname. Tot op heden zijn de resultaten van gedragsinterventies niet duidelijk. Er zijn geen positieve effecten van voedingssupplementen of gedragsstudies op longfunctie beschreven. Toekomstige studies

moeten onderzoeken welke groep patiënten het meest profijt heeft van gedragsinterventie en/of voedingssupplementen, waarbij het effect op de voedingstoestand en op het verloop in longfunctie wordt beoordeeld.

Hoofdstuk 3: Voedselinname van kinderen en adolescenten met cystic fibrosis

Een adequate voeding die nodig is voor het behalen en behouden van een goede groei, draagt bij aan de levensverwachting. De energiebehoefte van patiënten met CF kan verhoogd zijn door onder meer chronische luchtweginfecties en/of vetmalabsorptie. Daarom adviseren internationale CF-richtlijnen een energieverrijkt dieet, met innames tussen 110% en 120% van de aanbevolen dagelijkse hoeveelheid (ADH) voor energie, met een hoog energiepercentage vet. Echter, dit proefschrift toont dat kinderen en adolescenten uit deze groep een lagere energie-inname hebben dan het internationale advies. Echter, de absolute energie-inname was significant hoger dan die van gezonde referenten.

De ADH voor energie-inname is gebaseerd op het energieverbruik in rust, fysieke activiteit en een toeslag voor groei en zou de gemiddelde energiebehoefte van een bepaalde leeftijdscategorie gezonde personen dekken. Deze leeftijdscategorie omvat vaak 3 – 5 leeftijdsjaren. Het gebruik van zulke grote leeftijdsintervallen heeft beperkingen: wanneer een kind het eerste jaar van de volgende leeftijdscategorie bereikt, moet het volgens de aanbevelingen van de ene op de andere dag aanzienlijk meer energie consumeren om aan de ADH voor energie-inname te voldoen, terwijl in werkelijkheid de energie-inname van jaar tot jaar geleidelijk toeneemt. Verder verandert de energiebehoefte in de tijd als gevolg van een veranderde behoefte vanwege groei. Daarom is een ADH voor energie-inname voor elk afzonderlijk levensjaar in plaats van voor grote leeftijdscategorieën meer voor de hand liggend. Ook haalden de gezonde kinderen de ADH voor energie-inname uitsluitend in de eerste levensjaren, terwijl de kinderen in de oudere leeftijdscategorieën een inname lager dan de ADH hadden. Het is de vraag of de huidige ADH-aanbevelingen voor energie nog voldoen. Gezien de discrepantie tussen de ADH en de werkelijke energie-inname van gezonde referenten kan de energie-inname van patiënten met CF beter vergeleken worden met de werkelijke energie-inname per levensjaar van gezonde referenten en niet met de ADH.

Kinderen en adolescenten met CF hadden verder een significant hogere inname van vet en verzadigd vet in vergelijking met gezonde referenten. De inname van verzadigd vet was 12% – 14% van de totale energie-inname wat ruim boven de aanvaardbare bovengrens van 10% is.

Complicaties die verband houden met een overmatige inname van verzadigd vet, zoals hart- en vaatziekten kunnen een risico vormen, omdat de levensverwachting van patiënten met CF sterk verbetert. Het lijkt daarom verstandig om een deel van de verzadigde vetten in het dieet te vervangen door meervoudig onverzadigde vetten.

Hoofdstuk 4: Pancreasenzymtherapie en vetabsorptiecoëfficiënt van kinderen en adolescenten met cystic fibrosis

Patiënten met CF met een exocriene pancreasinsufficiëntie verliezen 50% – 80% van de geconsumeerde vetten, tenzij ze pancreasenzymtherapie krijgen. Verondersteld wordt dat, indien patiënten een juiste hoeveelheid pancreasenzymen innemen, vetopnames boven 85% en voor veel patiënten boven 90% kunnen worden behaald. Echter, onze studie vond vetopnames lager dan 85% in meer dan 20% van de metingen. Patiënten met een structurele vetopname lager dan 85% hadden een lager lichaamsgewicht dan de groep met een hogere vetopname.

De pancreasenzymdosering is gebaseerd op lipase-eenheden per gram geconsumeerd vet of op het lichaamsgewicht, met een maximale dosering van 10.000 lipase-eenheden/kg/dag. Waarschijnlijk geeft toediening boven deze maximale dosering geen verbetering in vetmalabsorptie en/of groei. Het is belangrijk de minimale dosis pancreasenzymen die nodig is voor een optimale vetopname voor te schrijven om zo de belasting van medicatie te beperken. Hierbij wordt de enzymdosering individueel bepaald, omdat blijkt dat patiënten verschillend reageren op een bepaalde dosering. Indien er sprake is van een blijvende significante vetmalabsorptie (vetopname lager dan 85%) dan moet onderzoek naar therapietrouw en/of andere factoren, zoals een lage zuurgraad in de darm of vertraagde motiliteit, worden overwogen.

Deel 2: Lichaamsgroei van kinderen en adolescenten met cystic fibrose

Hoofdstuk 5: De relatie tussen lichaamsgroei en longfunctie van kinderen met cystic fibrosis

Voedingstoestand en longziekte zijn nauw met elkaar verbonden, waarbij een suboptimale voedingstoestand is geassocieerd met een versnelde afname in longfunctie. Ook heeft een achterblijvende groei op jonge leeftijd consequenties voor de longfunctie op latere leeftijd.

In dit proefschrift is beschreven dat kinderen met een achterblijvend gewicht op de leeftijd van 2 jaar, maar met een gewichtstoename in de daaropvolgende jaren, een minder snelle

achteruitgang in longfunctie doormaken dan kinderen met een permanent achterblijvend gewicht.
Inhaalgroei voor gewicht lijkt gemakkelijker te realiseren dan inhaalgroei voor lengte.
Dit proefschrift beschrijft dat kinderen van 2 jaar met een achterblijvend gewicht of lengte wel toenemen in gewicht, maar achterblijven in lengte gedurende de 8 daaropvolgende jaren. Daarmee lijkt dat het achterblijven in lengtegroei op de leeftijd van 2 jaar mogelijk permanent is. Dit benadrukt het belang van het regelmatig evalueren van de voedingstoestand en het tijdig starten van voedingsinterventies bij een achterblijvende groei op jonge leeftijd.

Het bepalen van een lichaamsgewicht geeft geen inzicht in de samenstelling van het lichaamsweefsel en het is niet duidelijk of een gewichtsdaling of stijging het gevolg is van een toename/afname van vetmassa, vetvrije massa of beide. Deze kennis is noodzakelijk, omdat andere onderzoeken aantoonden dat vooral het verlies van vetvrije massa geassocieerd is met een afname in longfunctie. Het regelmatig bepalen van de lichaamssamenstelling is belangrijk om veranderingen veroorzaakt door groei, ziekte of voedingsinterventie te kunnen evalueren.

Hoofdstuk 6: Vergelijking van lengte-voor-leeftijd en lengte-voor-skelet-leeftijd met en zonder een correctie voor verwachte eindlengte van pediatrische patiënten met cystic fibrosis
De lengtetoename van een kind wordt beoordeeld door lengtemetingen te vergelijken met referentiemetingen van gezonde leeftijdsgenoten. Hiervoor wordt de uitkomst van de meting omgezet in een standaarddeviatie-score lengte-voor-leeftijd. Echter, de lengte-ontwikkeling wordt in belangrijke mate bepaald door de genetische aanleg. Wanneer hier niet voor wordt gecorrigeerd, kan een achterblijvende lengte onderschat worden bij kinderen met lange ouders en overschat worden bij kinderen met kleine ouders. Om misclassificatie te voorkomen is het daarom belangrijk dat lengtemetingen standaard worden gecorrigeerd voor de genetische component en dat dit structureel wordt opgenomen in de beoordeling van de lengtegroei van de pediatrische patiënt. Een lengtemeting houdt ook geen rekening met de botrijping van het kind, terwijl CF wordt gekenmerkt door een vertraagde botrijping als gevolg van de chronische ziekte en/of een suboptimale voedingstoestand. Dit proefschrift beschrijft een vertraagde botrijping van gemiddeld 2,7 maanden bij meer dan 60% van de patiënten en een vertraging van meer dan 1 jaar bij 20% van de patiënten. Het is daarom belangrijk om de botleeftijd te bepalen van die patiënten die na correctie voor de genetische component nog steeds een vertraagde lengtegroei laten zien.

Deel 3: Vitamine A en E inname van kinderen en adolescenten met cystic fibrosis

Hoofdstuk 7: Vitamine A en E inname van kinderen en adolescenten met cystic fibrosis

Patiënten met CF en een exocriene pancreasinsufficiëntie hebben een verhoogd verlies van vetten en, naar verondersteld wordt, ook van de vetoplosbare vitamines A en E, zelfs wanneer pancreasenzymtherapie wordt gegeven. Om deze reden adviseren internationale CF-richtlijnen standaard vitamine A en E voor te schrijven om tekorten te voorkomen.

Hoofdstuk 7.1: Vitamine A inname en serum vitamine A waarde van kinderen en adolescenten met cystic fibrosis

De vitamine A dosering zoals geadviseerd in de internationale CF-richtlijnen lijkt voldoende om tekort bij patiënten met CF te voorkomen. Het is echter de vraag of de aanbeveling te hoog is, omdat enkele studies een inname ver boven de aanvaardbare bovengrens voor gezonde referenten, en tevens (te) hoge serum vitamine A waarden bij meer dan 50% van de CF populatie tonen. Deze hoge inname kan nadelig en misschien zelfs gevaarlijk zijn. In onze retrospectieve studie kregen patiënten met CF 50% van de geadviseerde hoeveelheid vitamine A voorgeschreven, waarbij serum vitamine A waarden binnen de referentiewaarden bleven. Het lijkt dat de huidige dosering zoals geadviseerd in de internationale CF-richtlijnen hoger is dan nodig om een tekort te voorkomen. Het naleven van deze richtlijnen zou kunnen leiden tot een overdosering. Een vitamine A dosering overeenkomend met de helft van de aanbeveling met aanvankelijk een 6-maandelijkse evaluatie op basis van de serum vitamine A waarde is aan te bevelen. Als de serum vitamine A waarde stabiel en binnen de referentiewaarde is, kan een jaarlijkse evaluatie volstaan.

Hoofdstuk 7.2: Serum vitamine A waarde en longfunctie van kinderen en adolescenten met cystic fibrosis

In de literatuur wordt gesuggereerd dat verhoogd serum vitamine A waarden een beschermend effect op de longfunctie hebben. Dit is echter met de beschreven studie niet aangetoond. Wel is gevonden dat chronische ontsteking van invloed is op serum vitamine A waarden. Hoge serum immunoglobuline-G waarden, zoals bij chronische ontsteking, zijn namelijk geassocieerd met verlaagde serum vitamine A waarden. Daarbij waren hogere serum immunoglobuline-G waarden geassocieerd met lagere longfuncties. Het is daarom belangrijk om onderscheid te maken tussen verlaagd serum vitamine A waarden als gevolg van een insufficiënte vitamine A inname of als gevolg van een (chronische) ontsteking.

Hoofdstuk 7.3: Vitamine E inname, serum vitamine E waarde en longfunctie van kinderen en adolescenten met cystic fibrosis

De vitamine E dosering zoals geadviseerd volgens de internationale CF-richtlijnen lijkt eveneens ruim voldoende om tekort te voorkomen. In dit proefschrift wordt beschreven dat CF patiënten die 50% van de geadviseerde hoeveelheid vitamine E kregen serum vitamine E waarden binnen de referentiewaarden toonden. Daarom kan een dosering overeenkomend met de helft van de aanbeveling in eerste instantie gebruikt worden, met een 6-maandelijkse evaluatie op basis van de serum vitamine E waarde. Indien de serum vitamine E waarde stabiel en binnen de referentiewaarde is, kan een jaarlijkse evaluatie volstaan.
Er wordt gesuggereerd dat een verhoogd serum vitamine E waarde een beschermende werking heeft op de longfunctie. Echter, in dit proefschrift werd geen significante relatie tussen vitamine E waarden en longfunctie gevonden. Er is zelfs beschreven dat patiënten met een verhoogd serum vitamine E waarde een lagere longfunctie hadden hetgeen eerder een negatief effect suggereert.

Hoofdstuk 8: Conclusie

De levensverwachting van patiënten met CF is sterk verbeterd en zal dat ook de komende jaren zo blijven doen. De internationale CF-richtlijnen moeten op deze verbeterde levensverwachting afgestemd blijven. Ten aanzien van de energie-inname lijkt het voor de hand te liggen om een inname iets hoger dan die voor gezonde leeftijdsgenoten te adviseren, met individuele aanpassing voor patiënten met achterblijvende groei. Om risico op hart- en vaatziekten te beperken moet geadviseerd worden om de inname van verzadigd vet te minderen. Het is belangrijk om regelmatig de voedingstoestand te evalueren en tijdig te starten met voedingsinterventies bij patiënten met een achterblijvende groei. Om misclassificatie van de voedingsstatus te voorkomen moet standaard de lengtemeting gecorrigeerd worden voor de genetische component. Bij patiënten met achterblijvende lengte-groei is het bepalen van de botleeftijd belangrijk. Een vitamine A en E dosering overeenkomend met de helft van de aanbeveling van de internationale CF-richtlijnen kan in eerste instantie gebruikt worden bij het voorschrijven van vitamine A en E suppletie.

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Curriculum vitae

Acknowledgement

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Curriculum vitae

Janna Willemina (Willie) Woestenenk was born on May 2, 1972, in Lochem, the Netherlands. After completing her studies in Nutrition and Dietetics at the HAN University of Applied Sciences (1995), she has worked as a dietician at the department of Internal Medicine and Dermatology, Dietetics of the University Medical Centre Utrecht. During these years, she became more and more interested in research. This interest led to her undertaking part-time studies in Health Sciences at the University of Maastricht (2000 – 2003), alongside her work as a dietician. In the years after graduating, she continued working as a dietician and meanwhile started collecting data. The latter resulted in her first article.

In January 2012, Willie began working on the research described in this thesis, under the supervision of Prof. Dr. C.K. van der Ent and Dr. R.H.J. Houwen.

Willie lives with Arne Markink and together they have three children: Rutger (2003), Jort (2005) and Muriel (2007).