CHAPTER 2

ENERGY INTAKE AND GROWTH IN CYSTIC FIBROSIS PATIENTS WITH PRESERVED PULMONARY FUNCTION

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ABSTRACT
Improving the nutritional status remains an important challenge in pediatric cystic fibrosis (CF) patients. The effect of a high energy intake on the nutritional status in relatively healthy pediatric CF patients is not well described. We investigated the relation between energy intake, nutritional status and growth in school-age CF patients with preserved pulmonary function. In a cohort of Dutch CF patients, we analyzed data of 81 children with FEV1-values >80%. Patients below 6 and above 9 years were excluded to avoid inaccurate spirometric outcomes and growth interference during puberty respectively. We cross-sectionally assessed the relation between energy intake, nutritional status and growth (multiple-regression) and longitudinally evaluated the effect of changes in energy intake on weight (paired t-test). The nutritional status was slightly below average compared to the healthy reference population (z-score weight:-0.6±1.8, BMI:-0.1±0.7). Upon cross-sectional analysis, we found no positive relation between energy intake and nutritional status or growth. Upon longitudinal analysis, 19 patients increased their energy intake (10.2±9.8 kcal/kg/bw) in the year after the initial assessment, but the z-score for weight improved (0.18±0.16) in only 20% of the 19 patients. The positive effect of energy intake on weight was irrespective from the initial z-score for weight or the initial energy intake. Conclusion. The relation between energy intake, nutritional status and growth is weak in school-age CF patients with preserved pulmonary function. The results emphasize the need for individualized nutritional treatment, but simultaneously underline the difficulty to design nutritional trials with sufficient statistical power in this subgroup of CF patients.
INTRODUCTION

Cystic Fibrosis (CF) is an autosomal recessive disease and is caused by a mutation on the *Cftr* gene located on chromosome 7, which encodes for a chloride and bicarbonate channel in, particularly, epithelial cells. A defective CFTR protein results in the formation of viscous and sticky mucus with bacterial colonization, inflammation and eventually damage to different glands and gland rich organs. Intestinal malabsorption of nutrients (mainly due to pancreatic insufficiency), inadequate energy intake and increased energy expenditure due to recurrent pulmonary infections all contribute to a suboptimal nutritional status in CF patients. Since nutritional status is related to morbidity and mortality in CF, improving the nutritional status remains one of the important challenges in CF care.

The well known epidemiological study in Boston and Toronto of Corey et al. in the late '80s, introduced a major shift in the nutritional treatment of CF. The formerly restricted fat diet advised for CF patients, was changed into a high fat diet. Another major change comprised more aggressive pulmonary treatment and prevention of weight loss during infections. This renewed approach resulted in an improved nutritional status and overall survival of CF patients. Consequently, the current general CF dietetic recommendations comprises high dietary energy intakes ranging from 110-200% of the Recommended Daily Allowance (RDA) in patients with pancreatic insufficiency, in which energy derived from fat should be approximately 40%.

However, many children with CF have difficulties to meet the dietary recommendations. This phenomenon often creates a burden for CF children, parents and health care providers in their attempt to comply to the general recommendation. Nowadays, several studies report on adverse social and psychological consequences for CF patients and their families aiming to achieve high energy intakes, like family stress and feeding difficulties.

Since there are no conclusive studies which exclusively substantiated the potential beneficial effects of a high dietary energy intake in CF patients with preserved pulmonary function, we aimed to investigate the relation between dietary energy intake and nutritional status and growth in this subgroup of patients.

PATIENTS AND METHODS

We retrospectively evaluated data of pediatric CF patients who were under medical control on the 1st of January 2008 in the University Medical Centers in Utrecht and Groningen in the Netherlands. Both centers are specialized regional CF care centers. Patients visited the CF Center, at least annually, for a complete check up, consisting of a 72 hours fecal fat balance test, lung function test and a sputum culture test (if obtained). Children with FEV1 values above 80% were included in the study. Patients below 6 and above 9 were excluded to avoid inaccurate spirometry outcomes.
avoid pubertal growth effects respectively. For our cross-sectional analysis (n=81), the first recorded measurement for each child was used. In order to evaluate the effect of energy intake on weight (longitudinally), children from which complete datasets of at least two time points were available were included in the study (n=44) (Figure 1). The excluded children (n=37) had similar patient characteristics (parameters nutritional status, mutation class, co-morbidity etc) as the included children (data not shown). This study was deemed exempt by the University Medical Center Groningen and Utrecht Institutional Review Board.

Assessment of nutritional status
Weight (kg), length (cm) and BMI measurements of every child were collected. Annual growth velocity for length and weight were calculated using the charts of Tanner and Whitehouse. Growth velocity was defined as the increment in the child's length (cm/yr) and weight (kg/yr) divided by the time interval between the two measurements (with a minimum of 9 months and a maximum of 18 months). All growth parameters were converted into age-corrected z-scores based on Dutch national growth studies using “Growth analyzer 3” software of the Dutch Growth Foundation.

Assessment of energy intake
A three-day dietary diary was used to determine dietary intake of total energy. The dietary diaries contained three day prospective recorded household measurements with detailed information on macronutrient intake. We assumed that the dietary diary reflected the average daily dietary energy intake in the preceding year. All dietary diaries were manually processed by experienced specialized CF dieticians. The dietary

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**Figure 1. Flow chart.**
Flow chart for the retrospective analysis in pediatric CF patients between the age of 6-9 years with preserved pulmonary function (FEV1>80%). For the cross-sectional analysis, the first measurement of each child was used (n=81). For the longitudinal analysis, data available with at least two time points per child was used. The first two measurements per time point were selected (n=44). FEV1: Forced Expiratory Volume in 1 second.
energy intake of each child was expressed as a percentage of the RDA for gender and age\textsuperscript{14} and as kilocalories per kilogram body weight (kcal/kg/bw). Because energy intake expressed as a percentage of the RDA was age dependent (Figure 2A) and energy intake expressed as kilocalories per kilogram body weight was age independent (Figure 2B), we used the amount of kilocalories per kilogram body weight in our analysis as parameter for energy intake.

Relation between energy intake, nutritional status and growth

Cross-sectional analysis. Based on the first available measurement of each child in the age group 6-9 years, we cross-sectionally evaluated energy intake in relation to the z-scores of weight, length, BMI, weight gain and length growth. Apart from energy intake, several other factors, like fat absorption, \textit{Cftr} mutation, age and gender are expected to influence nutritional status and growth. Therefore, we evaluated these parameters as additional patient factors for analysis. The coefficient of fat absorption was calculated as: (fat intake – loss of fecal fat) / fat intake * 100\%. \textit{Cftr} gene mutations were divided in five classes based on their demonstrated or presumed molecular consequences [19].

Longitudinal analysis. We evaluated the effect of an increased or decreased energy on the z-score for weight. For this purpose we calculated the difference between the energy intake and the z-score for weight between two time points; the first measurement per child was called time point 0 (T\textsubscript{0}) and the second measurement was called time point 1 (T\textsubscript{1}). The mean time interval between the two time points was 1.2 ± 0.4 years. In order to specifically conclude about the effect of energy intake in patients with a suboptimal nutritional status, we made the comparison between patients with initial (i.e. at T\textsubscript{0}) z-scores for weight below or above 0. In addition, we evaluated whether the effect of an increased or decreased energy intake on weight was dependent upon the initial amount of energy intake.

\textbf{Figure 2. Sub-analysis energy intake at different ages.}
\textit{A}) Energy intake expressed as RDA (Recommended Daily Allowance). \textit{B}) Energy intake expressed as kilocalories per kilogram body weight (kcal/kg/bw). Values are depicted as mean ± SEM. ** = p<0.01 (compared to age 6, 7 and 8).
Statistical analysis
Statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL). Cross-sectional analysis. The relation between energy intake and nutritional status and growth was cross-sectionally assessed by linear regression analysis. A stepwise multiple regression analysis was performed to correct for confounding effects on nutritional status and growth. The analysis included z-scores for weight, length, BMI, weight gain and length growth as dependent variables and were tested for normal distribution. Total energy intake, fat absorption (%), mutation class, age and gender were used as independent variables. We repeated the analysis and replaced the variable ‘total energy intake’ for the variable ‘energy intake of fat’. The different Cftr mutation classes were included in the multiple regression analysis by transforming them into dummies and by using the enter method. Longitudinal analysis. We longitudinally evaluated the effect of an increased or decreased energy intake (compared to the previous year) on the z-score for weight by using the paired student t-test. All data are reported as means ± the standard deviation (SD). P-values < 0.05 were considered as statistically significant.

RESULTS

Characteristics study group
Table 1 shows the patient characteristics for the cross-sectional as the longitudinal analysis for several parameters. Parameters were similar between the cross-sectional and the longitudinal data. All patients within our cohort were pancreas insufficient and were treated with pancreatic enzymes. The overall nutritional status was slightly below average compared to the healthy reference population according to length, weight and BMI. Growth velocity scores were above average for length as well as weight. The mean total energy intake and the percentual energy intake derived from fat in our cohort of pediatric CF patients was comparable to the general CF nutritional recommendations of 120-150% [28]. Except for meconium ileus, with a higher incidence in males, gender was equally distributed among the other parameters.

Relation between energy intake and nutritional status (cross-sectional analysis)
Although the mean z-scores for nutritional status in our cohort of patients was slightly below average compared to the healthy reference population (Table 1), the z-score for weight was below zero in 78% of patients (Figure 3). We found no relation between total energy intake or fat intake and z-scores for weight, length, BMI, weight gain and length growth (Figure 3). A weak negative association was found between total energy intake and the z-score for weight (R=0.27, p=0.02). The multiple regression analysis, that included several potential confounding factors on nutritional status or growth (fat absorption, mutation class, age and gender), showed no dependency on these results. The z-score for BMI was positive associated with age (R = 0.22, p=0.03).
### Table 1. Patient characteristics.

Baseline characteristics of cross-sectional and longitudinal data of pediatric cystic fibrosis patients with preserved pulmonary function (defined as FEV1 values > 80%). Z-scores for weight and length are depicted as z-scores for age. Cross-sectional and longitudinal values for all parameters were not statistically different from each other. Ursodeoxy-cholate was prescribed because of suspicion of CF related liver disease, based on persistent increased serum trans-aminases, hepato-megaly and/or hepatic ultrasound abnormalities (40-41). CFTR gene mutations were divided in five classes based on their demonstrated or presumed molecular consequences (19).

FEV1: Forced Expiratory Volume in 1 second. RDA: Recommended Daily Allowance. Kcal/kg/bw: kilocalories per kilogram body weight. Parameters are reported as a percentage or as mean ± SD.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cross-sectional (n=81) (% or mean±SD)</th>
<th>Longitudinal (n=44) (% or mean±SD)</th>
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<tbody>
<tr>
<td>Age</td>
<td>7.4 ± 1.2</td>
<td>7.0 ± 0.8</td>
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<td>Gender, f (%)</td>
<td>49</td>
<td>45</td>
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<td><strong>Dietary energy intake</strong></td>
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<td></td>
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<tr>
<td>% RDA</td>
<td>117 ± 25</td>
<td>121 ± 26</td>
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<tr>
<td>% Fat</td>
<td>35 ± 5</td>
<td>36 ± 6</td>
</tr>
<tr>
<td>% Carbohydrate</td>
<td>52 ± 6</td>
<td>51 ± 6</td>
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<tr>
<td>% Protein</td>
<td>13 ± 2</td>
<td>13 ± 2</td>
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<tr>
<td>Kg/kg/bw, total</td>
<td>85 ± 14</td>
<td>85 ± 11</td>
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<td>Kg/kg/bw, fat</td>
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<td>30 ± 6</td>
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<tr>
<td>Kg/kg/bw, carbohydrate</td>
<td>44 ± 9</td>
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<tr>
<td>Kg/kg/bw, protein</td>
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<td>11 ± 2</td>
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<td>Z-score length</td>
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<td>-0.6 ± 1.0</td>
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<td>Z-score weight</td>
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<td>-0.6 ± 0.9</td>
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<tr>
<td>Z-score BMI</td>
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<td>-0.1 ± 0.7</td>
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<tr>
<td>Z-score length growth</td>
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<td>Z-score weight gain</td>
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<td>FEV1, %</td>
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<td>Meconium ileus (%)</td>
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<tr>
<td>Distal ileal obstruction syndrome</td>
<td>7</td>
<td>9</td>
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<td>% Fat absorption</td>
<td>91± 9</td>
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<td>Pancreatic enzymes (%)</td>
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<td>Ursodeoxycholate (%)</td>
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<tr>
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<td>Homozygous ΔF508 (%)</td>
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<tr>
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The effect of an increased or decreased energy intake on z-score weight (longitudinal analysis)

In correspondence with the cross-sectional results, we found no relation between energy intake and the z-score for weight in the longitudinal analysis (Figure 4). Out of the 44 patients, 17 increased their energy intake in the year after the initial assessment (mean increase 10.2±9.8 kcal/kg/bw), but only 4 of these patients showed a corresponding improvement in the z-score for weight (right upper quadrant in Figure 4A), while the majority of patients showed a stabilization or decrease in the z-score for weight (right lower quadrant in Figure 4A). A decrease in energy intake in the year after the initial assessment (mean decrease 13.3±9.5 kcal/kg/bw) in 27 of patients, resulted in a corresponding decrease in the z-score for weight in roughly 50% of these patients, while the other 50% of patients showed an improvement (left lower and upper quadrant in Figure 4A, respectively).

Figure 3. Relation between energy intake and nutritional status (cross-sectional analysis).
Upper panel: relation between total energy intake and z-scores for weight (A), BMI (B), and weight gain (C). Lower panel: relation between fat intake and z-scores for weight (D), BMI (E), and weight gain (F). kcal/kg/bw: kilocalories per kilogram body weight. R: correlation coefficient.
To examine these results in more detail, we additionally investigated whether the effect of an increased or decreased energy intake on weight after a year of the initial assessment, depended on the initial z-score for weight or on the initial amount of energy intake. We subdivided patients with initial z-scores for weight above or below 0. The subdivision did not affect the longitudinal relation between energy intake and z-score for weight (Figure 5). We found a decrease in z-score for weight in patients with initial high z-scores for weight during increased energy intake (n=5; Figure 5B). When subdividing patients with initial energy intakes above and below 90 kilocalories per kilogram body weight, we neither found a difference between an increased or a decreased energy intake concerning the effect on the z-score for weight (data not shown).

Figure 4. Relation between delta energy intake and delta z-score for weight (longitudinal analysis).
A) Relation between the difference (Δ) in annual energy intake and the corresponding annual difference in z-score for weight. B) Percent distribution of patients with increased or decreased energy intake after a year of the initial assessment and the corresponding effect on the z-score for weight. kc/kg/bw: kilocalories per kilogram body weight. R: correlation coefficient. ↑: increased, ↓: decreased, ↔: not changed.

The effect of an increased energy intake on z-score weight

The effect of a decreased energy intake on z-score weight

Figure 5. The effect of an increased or decreased energy intake on z-score weight.
In order to conclude about the effect of an increased (A-B) or decreased (C-D) energy intake in relation to the initial nutritional status of CF patients, patients were categorized according to their initial z-score of weight (below or above 0) at time point 0 (T0). Figures A and C depicts the actual increase or decrease in energy intake in kilocalories per kilogram body weight (kcal/kg/bw) in the following year (T1). Figures B and D depicts the effect of the increased or decreased energy intake on z-score weight in the following year (T1). Values are depicted as mean ± SD. * : p-value < 0.05 (comparing T0 with T1).
DISCUSSION

Our study is the first which exclusively investigated the relation between energy intake and nutritional status and growth in school-age pediatric CF patients with a preserved pulmonary function. We found that approximately 80% of CF children have a z-score for weight below zero, despite preservation of pulmonary function. However, retrospective evaluation, in a cross-sectional and longitudinal setting, showed no relation between energy intake and nutritional status or growth.

Until now, most studies evaluated the relation between energy intake and either nutritional status or growth in pediatric CF patients who already are in a more advanced stage of disease \(^1, 4, 13, 15, 18-19, 22, 27, 30-33, 36, 38\) (e.g. patients with impaired pulmonary function and/or patients who are more severely malnourished). From retrospective studies we learned that, in this group of CF patients, a weak correlation \((R < 0.55)\) existed between energy intake and nutritional status.\(^1, 4, 13, 18\) A more pronounced effect of dietary energy intake on nutritional status and growth is often reported in nutritional intervention studies.\(^12, 27, 36, 38\) It is also shown that only a small beneficial effect on nutritional status occurs in CF patients who were in a better nutritional condition.\(^33\) This observation is in agreement with the data from Shepherd et al. indicating that a significant correlation existed between initial underweight and subsequent weight gain after nutritional intervention in CF patients during pulmonary exacerbation.\(^27\) In addition, most nutritional intervention studies are performed in patient groups with initial low dietary energy intakes \((\leq 120\% \text{ of the RDA})\) . Constantini et al. showed that when dietary energy intake is equal to or higher than 95\% of the RDA wasting does not occur \([5]\). Based these observations, in our present study, we subdivided our patients according to their initial z-score for weight and initial energy intake. However, this subdivision did not affect the observed lack of correlation between energy intake and either nutritional status or growth.

We do realize that our present data should be interpreted in light of some limitations. First, a three day dietary diary can not be expected to completely represent the actual average daily dietary energy intake over the previous year, but, at best, constitutes a rough estimate. The obtained results may be biased by over- or underestimation in the report of the three-day registration period (for example during weekend registrations). Also, detailed information on some of the nutrients in the diaries may be absent. This limitation can lead to inaccuracies in the calculation of the absolute quantity of caloric intake. Although we realize that our study can be affected by these factors, it should be underlined that the reported dietary energy intakes were comparable to those obtained in other studies.\(^11-12, 21, 34\) Previous retrospective studies, in more severely affected CF patients, also used three-day dietary diaries as measurement for energy intake.\(^1, 4, 13, 18\) A second limitation of our study is the absence of data on energy expenditure or other parameters for nutritional status (for example fat free mass). As growth is influenced by a complex interaction between energy demand and energy expenditure, the absence of these data may bias our results. However, we did evaluate a relatively homogenous
subgroup of patients; all of our patients were pre-pubertal, had preserved pulmonary function and suffered from pancreatic insufficiency. Each of these factors might have a major influence on resting energy expenditure and growth\(^40\), but it seems reasonable to expect that these parameters were comparable between patients. In addition, we analyzed for possible influence of several other parameters on the observed correlations in our multiple regression analysis (e.g. gender, age, mutation class). Yet, neither of these parameters seemed to affect our results.

Since the CF nutritional recommendations still comprises high energy intakes for all pediatric CF patients, our data support the concept that sub-analysis of different groups of CF patients is necessary to categorize or even individualize the dietary advices. We believe it is important to investigate the relatively healthy CF patients with preserved pulmonary function, to conclude whether the actual beneficial effects on nutritional status or growth outweigh the possible adverse physiological consequences in our strive to achieve high dietary energy intakes. Our retrospective analysis in school-age CF patients with preserved pulmonary function indicates no straight-forward relation between energy intake and nutritional status or growth. We do believe that our data supports the need for prospective nutritional studies in this subgroup of CF patients, but our results simultaneously underline the difficulty to design such nutritional trials with sufficient statistical power.

REFERENCES


