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Effect of Selected Factors Associated with the Clinical Course of the Disease on Nutritional Status in Children with Cystic Fibrosis

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. Malnutrition and delayed growth are commonly seen in children with cystic fibrosis and are indicators of poor prognosis. Understanding the factors that affect growth and nutritional status may improve care, treatment and longevity.
Objectives. To determine how nutritional status, as estimated using anthropometric measurements, in children with cystic fibrosis is affected by 1) the type of *CFTR* mutation, 2) colonization by *Pseudomonas aeruginosa,* and 3) age at diagnosis. The relationship between nutritional status and pulmonary function was also investigated.
Material and Methods. Anthropometric data on height, weight, circumferences and skinfold thicknesses were extracted from the medical histories of 41 boys and 48 girls diagnosed with cystic fibrosis who were treated at the Institute of Mother and Child in Warsaw, Poland. Muscle and fat tissue area were calculated from these measurements. The values for children with CF were compared to the Polish national growth reference charts. Multivariate linear regression tested the effect of three factors on nutritional status: colonization with *P. aeruginosa*, age at diagnosis, and the type of *CFTR* mutation.
Results. All values for children with CF were significantly lower than in the reference population. The results show that, in the children examined, nutritional status is more adversely affected than growth. Of the factors related to the clinical picture of the disease, only the presence of respiratory tract colonization by *P. aeruginosa* had an effect on physical development in the children examined. Neither the type of mutation present nor age at diagnosis had any significant effect.
Conclusions. Chronic colonization by *P. aeruginosa* interfered with growth and markedly worsened nutritional status, and was also associated with reductions in both total and lean body mass. Early nutritional intervention can improve nutritional state and pulmonary function in children with CF (**Adv Clin Exp Med 2014, 23, 5, 775–783**).

Key words: cystic fibrosis, anthropometry, malnutrition, muscularity, *Pseudomonas aeruginosa.*

Cystic fibrosis (CF) is the most common autosomal genetic disease in white children, and can lead to premature death. CF is a multi-system disease that presents most often as bronchio-pulmonary disease and pancreatic enzymatic insufficiency, accompanied by digestive and absorption disorders. It occurs in one in 4,400 live births [1]. The disease is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene on Chromosome 7, which codes for the protein that regulates chloride ion transport by epithelial cells. At this time, more than 1,900 mutations affecting the CFTR gene have been identified [2]. The main cause of death is impaired respiratory function. Nutritional status is one of the most important prognostic factors for the course of the disease and the expected lifespan of CF sufferers [3]. Nutritional status acts independently of pulmonary function. In one study, when body weight fell below 85% of the ideal, there was

a significant increase in the probability of death within the next five years [4]. Early intensive nutritional intervention improves the function of the respiratory system, thereby prolonging the lifespan of affected individuals [5, 6].

In spite of the enormous progress that has been made in the diagnosis and treatment of CF, poor nutrition is still a common consequence and significant problem [3]. Routine assessment of the nutritional status of affected individuals is usually limited to indicators based on body height and body weight such as percentage of ideal body weight (% IBW) or body mass index (BMI). Weight/height ratio is not, however, a reliable indicator of nutritional status in individuals with CF because it masks deficits in body mass and cannot be used to estimate the tissue composition of the body [7, 8]. In fact, the weight/height ratio may indicate a normal nutritional state even in individuals with a deficit of lean body mass. Body weight deficit is then masked by the presence of abdominal ascites and peripheral edema [9, 10].

The course of the disease is also thought to be strongly influenced by several non-nutritional factors. Among them are the type of CFTR mutation present, reoccurring respiratory tract infections, the age at the time of diagnosis, and familial socioeconomic conditions [11–14].

The mutation most commonly seen in the population of Poland is F508del, which is associated with a high risk of premature demise [1]. The presence of this mutation in both alleles of the CFTR gene causes a severe course of the disease.

Individuals with more benign mutations are usually diagnosed later in life than individuals who are homozygous for F508del. They have a lower concentration of chloride in their sweat, have better pulmonary efficiency, are better nourished, have a lower pancreatic exocrine deficiency index, and also suffer less often from respiratory tract infections caused by *P. aeruginosa* [15].

The aim of the present study was to determine how nutritional status in children with cystic fibrosis is affected by 1) the type of CFTR mutation, 2) colonization by *Pseudomonas aeruginosa,* and 3) age at diagnosis. An expanded array of somatic measurements and indices was used to estimate nutritional status and body composition. The relationship between nutritional status and pulmonary function was also investigated.

Material and Methods

The patients included in the present study were those between 6 and 18 years of age seeking treatment from January through December, 2006, at the Institute of Mother and Child in Warsaw, Poland. All such children were invited into the study sample, and were included if their parents consented. The study protocol was approved by the ethics committee of the Institute (No. 8/2010). Written informed consent for somatic measurements and participation in the survey was obtained from the parents of each subject.

All children were treated in accordance with current CF treatment standards [16]. Alimentary therapy included diet modification with vitamin and enzyme supplements. Other therapy included physiotherapy, nebulizer treatments for bronchopulmonary complications, and antibiotics for chronic infection by *Pseudomonas aeruginosa*.

The sample consisted of 41 boys and 48 girls. The mean age of the children was 12.3 ± 3.5 years. Cystic fibrosis was confirmed by positive sweat tests. All subjects were Caucasian. 90% of the children suffered from secretory pancreatic enzymatic deficiency. 6% suffered from diabetes, 4% from cirrhosis of the liver, and 3% from non-alcoholic steatohepatitis. The mean age at the time of CF diagnosis was 3.0 ± 3.8 years. 29% were diagnosed immediately after birth. 36% were diagnosed when they were three months to three years old, 35% were diagnosed after they were three years old.

Anthropometric parameters were measured by trained anthropologists in accordance with the procedures described by Martin and Knusmann [17]. The following data was recorded: height, weight, triceps skinfold thickness, subscapular skinfold thickness, abdominal skinfold thickness, the sum of the three skinfold thicknesses, and upper arm circumference. Height was measured to an accuracy of 1 mm. Weight was measured to an accuracy of 0.1 kg. Skinfold thicknesses were measured with an instrument produced by HOLTAIN to an accuracy of 0.2 mm.

Nutritional status was estimated using lean muscle and fat mass. Weight/height ratio and body mass index (BMI) served as indicators of relative weight. BMI was calculated by dividing the weight in kilograms by the square of the height in meters. Children were classified as undernourished if they had a BMI less than the tenth percentile, properly nourished if they had a BMI between the 10^{th} and 90^{th} percentiles, and overweight if they had a BMI greater than the ninetieth percentile.

Upper arm muscle circumference (AMC) was calculated using the following formula [18]:

$$AMC = AC - (\pi \times TST),$$

where AC represents arm circumference and TST represents triceps skinfold thickness.

Body composition was estimated using upper arm muscle area and upper arm fat tissue area.

Upper arm muscle area (UAMA) was calculated using the following formula [18]:

$$UAMA = [AC - (\pi \times TST)]^2.$$

Upper arm fat tissue area (UAFTA) was calculated using the following formula [18]:

$$UAFTA = UAA - UAMA,$$

where UAA represents upper arm area.

DNA was analyzed in order to determine the type of CFTR gene mutation. The studies were carried out upon admission at the Medical Genetics Laboratory of the Institute of Mother and Child. Three groups were identified. 52% had the genotype F508del/F508del, 34% had the genotype F508del/ /Mt, and 15% had the genotype Mt/Mt, where Mt represents any mutation other than F508del.

Microbiological tests for colonization by *P. aeruginosa* were performed on sputum specimens. If negative, they were repeated on deep swabs of the throat. Colonization was classified in accordance with the diagnostic criterion proposed by Lee et al. [19]. In the twelve months prior to the study, 38% of the children showed no signs of colonization, 18% were positive for intermittent colonization and 44% were positive for chronic colonization.

Spirometric measurements were performed during routine check-up visits at three to six month intervals. The data recorded included Forced Vital Capacity (FVC), Forced Expiratory Volume in one second (FEV_1) and Forced Expiratory Flow (FEF_{25-75}). All spirometric parameters were measured using a MES JAEGER 100 spirometer in accordance with the procedures recommended by the Polish Phthisiopneumological Society. All results were recorded as percentages of the predicted values, standardized for age, gender and height [20, 21].

Statistical Analysis

Anthropometric parameters were expressed in terms of standard deviations of the age-specific and sex-specific reference values published in Polish national growth reference charts [18]. Differences between the children and the reference population were evaluated using Student's *t*-test for single samples. The results for pulmonary function tests were differentiated according to nutritional status. Sex differences were also evaluated using Student's *t*-test or, for asymmetrical distributions, the Mann Whitney test. Asymmetry of distributions was evaluated using the Shapiro-Wilk test. The relationship between type of CFTR mutation and prevalence of colonization by *P. aeruginosa* was compared using the χ^2 test.

The effect of selected factors associated with the course of the disease on somatic development was determined using multi-variate regression analysis. Dependent variables describing the status of physical development included all of the somatic traits and indices. The independent values describing the course of the disease included CFTR mutation type, respiratory tract colonization by *Pseudomonas aeruginosa*, and age at time of diagnosis. Standardized beta cofactors were used to facilitate comparison of the strength of the correlation of individual independent values with those dependent variables recorded using different units.

Differences were considered significant at $p < 0.05$. All analyses were carried out using the STATISTICA 10.0 software package.

Results

The mean standardized values for the anthropometric and spirometric parameters were calculated using the values for the reference population (Tables 1 and 2). All of the somatic traits, body mass indices, and body composition indicators differed significantly from the reference values, except for abdominal skinfold thickness. Mean weight, weight/ /height ratio and BMI were all significantly lower in the children than in the reference population. 33% of the children were undernourished, of which half were severely malnourished with a BMI less than the third percentile. One of the girls was obese with a BMI greater than the 97th percentile (Fig. 1–4).

In addition, the children studied were significantly shorter than their healthy peers (Table 1). 11% were shorter than the third percentile. Pulmonary function parameters were significantly worse in undernourished individuals than in normally nourished ones (Table 3). There were no differences in values for pulmonary function parameters between boys and girls (Table 2).

Deficits in body mass were related to both limited body fat content and decreased development of lean body mass, or muscle tissue mass. This is indicated by the values for skinfold thickness, especially the triceps and subscapular skinfold thickness, as well as upper arm circumference and upper arm circumference without adipose tissue.

There was no significant relation between the type of CFTR mutation and prevalence of colonization by *P. aeruginosa* ($\chi^2 = 6.203$, df = 4, $p = 0.184$). The results of regression analysis reveal a strong correlation between the prevalence of colonization and all anthropometric parameters reflecting nutritional status. No such correlation was found between the type of CFTR mutation and nutritional status, nor between age at time of diagnosis and

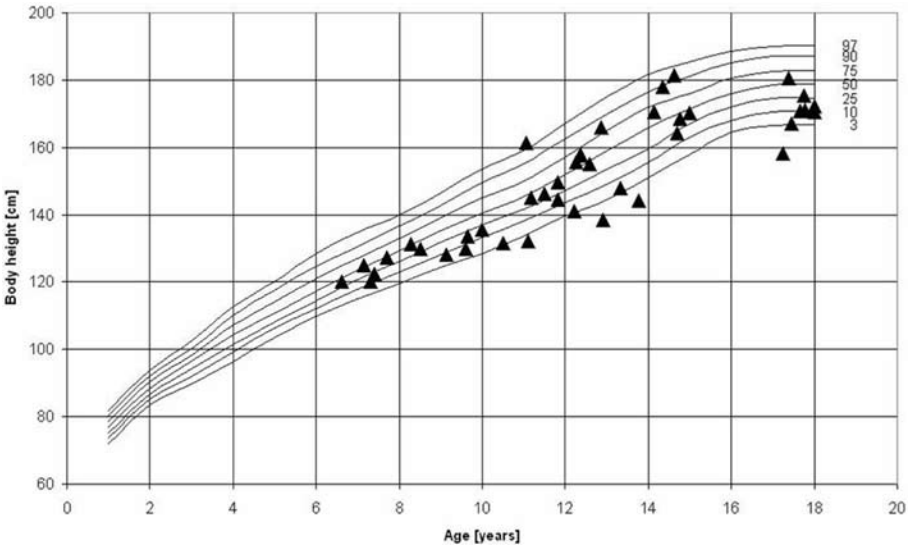

Fig. 1. Percentile chart of body height of CF boys

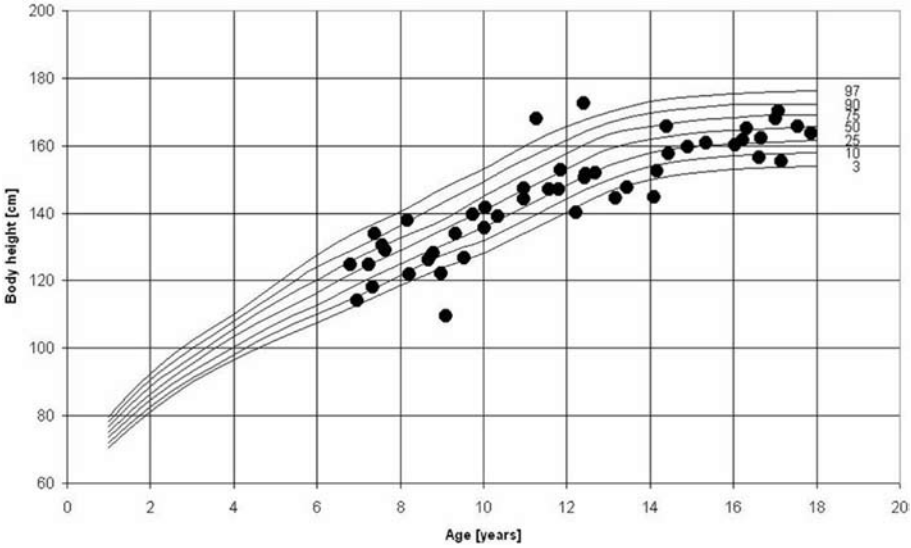

Fig. 2. Percentile chart of body height of CF girls

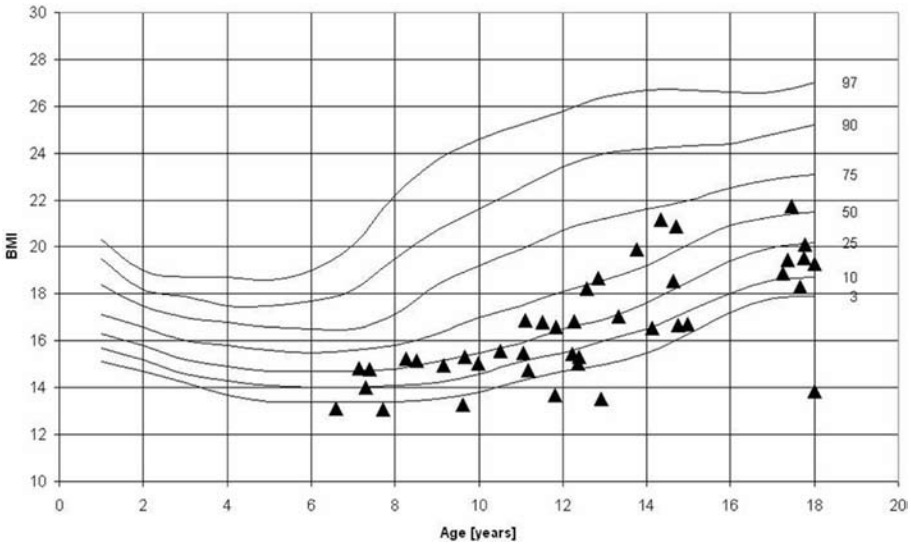

Fig. 3. Percentile chart of BMI of CF boys

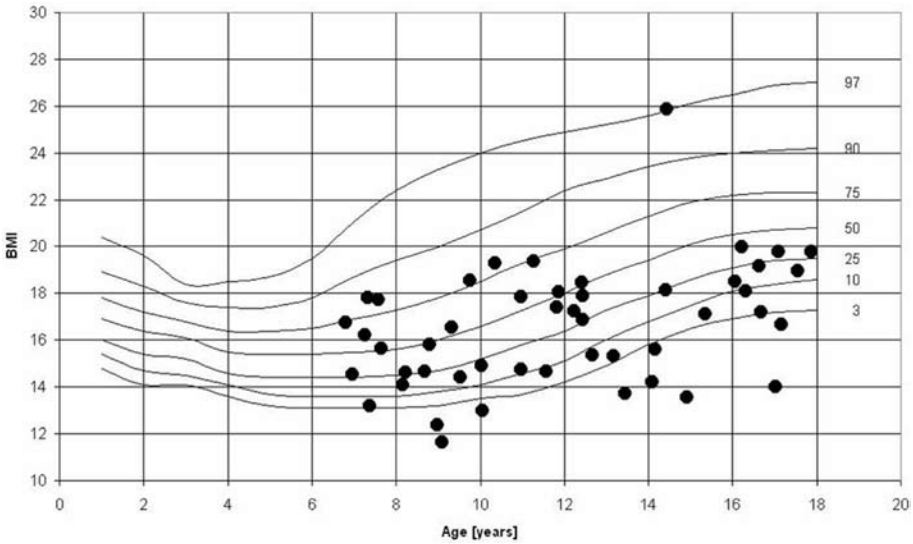

Fig. 4. Percentile chart of BMI of CF girls

Table 1. Anthropometric parameters in children and adolescents with cystic fibrosis, expressed in terms of standard deviations away from the means of reference values for the population of Poland

Parameter	Mean ± SD	Range	P
Body height	–0.57 ± 1.25	–4.21–2.96	< 0.001
Body weight	–0.85 ± 0.89	–2.81–1.98	< 0.001
Body mass index	–0.77 ± 0.79	–2.90–2.37	< 0.001
Weight/height ratio	–0.68 ± 0.78	–2.86–1.65	< 0.001
Triceps skinfold thickness	–0.70 ± 0.76	–2.40–1.94	< 0.001
Subscapular skinfold thickness	–0.34 ± 1.12	–1.73–5.13	< 0.01
Abdominal skinfold thickness	0.13 ± 1.48	–1.83–5.45	> 0.05
Sum of three skinfold thicknesses	–0.34 ± 1.09	–2.11–5.52	< 0.01
Upper arm circumference	–0.87 ± 0.96	–3.12–2.26	< 0.001
Upper arm muscle circumference	–0.75 ± 1.01	–3.23–1.81	< 0.001
Upper arm muscle area	–0.70 ± 0.93	–2.70–2.04	< 0.001
Upper arm fat tissue area	–0.70 ± 0.71	–2.04–2.30	< 0.001

Table 2. Percent of predicted forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and forced expiratory flow (FEF_{25-75}), standardized for age and sex

Percent of predicted value	Boys (n = 41)	Girls (n = 48)	P value
FVC%	81.46 ± 19.32 (39 to 116)	80.71 ± 19.48 (33 to 123)	0.866[a]
FEV_1%	79.91 ± 23.08 (31 to 114)	81.09 ± 23.67 (32 to 119)	0.634[b]
FEF_{25-75}%	78.17 ± 37.81 (11 to 145)	68.54 ± 34.15 (13 to 136)	0.307[b]

[a] Student's *t*-test.
[b] Mann-Whitney test.

Table 3. Percent of predicted forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and forced expiratory flow (FEF_{25-75}) by nutritional status

Percent of predicted value	Undernourished (n = 29)	Properly nourished and obese (n = 59 + 1)	P value
FVC%	71.44 ± 19.68	85.43 ± 18.40	0.003[a]
FEV_1%	69.04 ± 24.76	85.57 ± 21.13	0.006[b]
FEF_{25-75}%	62.60 ± 38.82	78.63 ± 34.33	0.105[b]

[a] Student's *t*-test.
[b] Mann-Whitney test.

Table 4. Regression analysis for three selected factors related to the clinical picture of CF

Parameter	Age at time of diagnosis[a]		Type of CFTR mutation[b]		Colonization by *P. aeruginosa*[c]	
	Beta	p	Beta	p	Beta	p
Body height	–0.211	0.0561	–0.006	0.9545	–0.216	0.0431
Body weight	–0.058	0.5889	0.073	0.4904	–0.317	0.0031
Body Mass Index	0.077	0.4720	0.048	0.6511	–0.294	0.0059
Weight/height ratio	0.158	0.1468	0.065	0.5441	–0.211	0.0469
Triceps skinfold thickness	–0.116	0.2746	–0.052	0.6164	–0.344	0.0012
Subscapular skinfold thickness	0.012	0.9125	0.005	0.9626	–0.215	0.0475
Abdominal skinfold thickness	–0.118	0.2752	0.202	0.0607	–0.257	0.0151
Sum of three skinfold thicknesses	–0.059	0.5843	–0.136	0.2098	–0.277	0.0100
Upper arm circumference	0.002	0.9876	–0.084	0.4217	–0.350	0.009
Upper arm muscle circumference	0.052	0.6296	–0.089	0.4048	–0.294	0.0059
Upper arm muscle area	0.066	0.5397	–0.076	0.4765	–0.286	0.0074
Upper arm fat tissue area	–0.088	0.4012	–0.056	0.5945	–0.359	0.0007

[a] (more than 3 years old, 3 months to 3 years old, immediately after birth).
[b] (F508del/F508del, F508del/Mt, Mt/Mt).
[c] (chronic colonization, intermittent colonization, no signs of colonization).

nutritional status (Table 4). Negative values for the beta coefficient indicate that the mean values for all of the somatic parameters related to nutritional status consistently decreased with increasing prevalence of colonization. Anthropometric parameters reflecting nutritional status and body tissue composition were strongly affected in colonized children, with the lowest values in chronically colonized children (Table 4, Fig. 5).

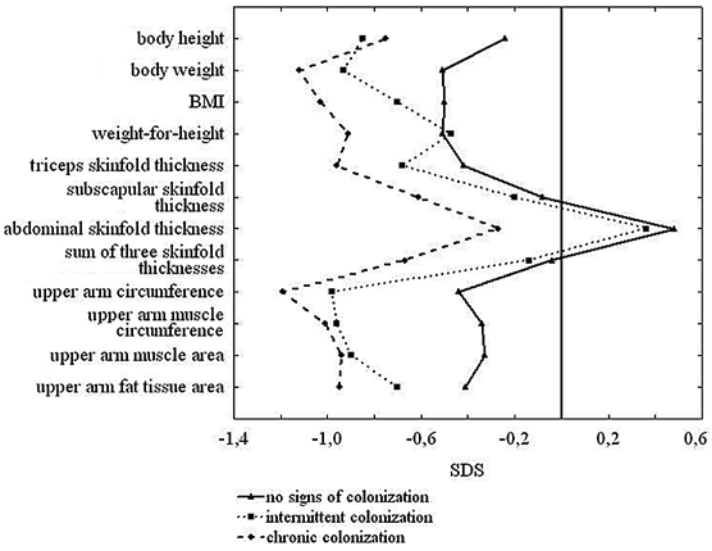

Fig. 5. Mean standardized values for somatic traits in the children examined in the present study in relationship to the status of respiratory tract colonization by *Pseudomonas aeruginosa*

Discussion

Measurement of somatic traits and the indices calculated using them permit an accurate assessment of growth rate, nutritional status and body composition in children with CF. In the affected children in this study, nutritional status was more adversely affected than growth. Similar results were obtained in other studies conducted in the last ten years on children who were diagnosed and treated in clinics in Poland that specialize in treating patients with CF [12, 22, 23]. Some researchers are of the opinion that the high prevalence of malnutrition in children with CF is largely because individuals with the most severe form of the disease are now surviving longer than ever before [24].

In the present study, 33% of the children with CF were underweight, whereas only about 1% were overweight. Malnutrition resulted in a thinning of the layer of subcutaneous adipose tissue and a reduction in body musculature. Malnutrition was correlated with worse results for FVC% and FEV_1%. Early effective nutritional intervention therefore significantly delays the development of pulmonary complications in children with CF. In one study, pulmonary function parameters and longer lifespan were correlated with body mass at age 4 [25].

In the present study, there was no correlation between the type of CFTR mutation and nutritional state. On the other hand, a previous study in Poland found that nutritional status was significantly worse in children who were homozygous for CFTR mutation type than in heterozygous individuals. Children who were homozygous for F508del were diagnosed earlier than those who were homozygous for other mutations [12]. Based on data gathered by the CF Twin-Sibling Study and the Cystic Fibrosis Foundation Patient Registry in the United States, BMI is affected more by other genes on chromosomes 1 and 5 than by mutations in the CFTR gene, which is on chromosome 7 [26].

In the present study, physical development was most disordered in children with chronic respiratory tract colonization by *P. aeruginosa,* the most common respiratory tract pathogen in individuals with CF. It is found in 20 to 40% of young children, and over 80% of adults with cystic fibrosis [27]. Numerous studies have examined the effect of colonization by *P. aeruginosa* on the clinical picture of individuals with cystic fibrosis. These studies revealed a rapid drop in FEV_1 and a worsened state of the respiratory system as revealed by radiography in both children and adults [28, 29]. Other findings include more frequent hospitalization, increased risk of death, and shorter survival time in colonized individuals than in non-colonized individuals with cystic fibrosis [30].

In the present study, colonization of the respiratory tract by *P. aeruginosa* was correlated with a large deficit in nutritional status in the children examined, especially in those with chronic colonization. This was associated with a deficit in both adipose and muscle tissue. The results of studies on the effect of colonization of the respiratory tract by *P. aeruginosa* on somatic development are, however, conflicting.

In a longitudinal study monitoring physical development in 139 children with CF from birth to age 19, colonization had no detectable effect on growth rate, but chronic infection caused a marked worsening in nutritional status [9].

In another long-term study on growth rate in about 200 children with CF, the growth rate was significant lower in children with chronic infection than in children without colonization of the respiratory tract by *P. aeruginosa*. The growth rate was 5.63 cm/yr in chronically infected children, and 6.96 cm/yr in uncolonized children [28]. The authors of that study observed, however, that most of the children with CF they examined, regardless of infection status, developed within the norm for the health population as far as body height and body mass were concerned.

In a preliminary study on children in a screening program for CF, neither body height nor body mass up to age 7 differed significantly between those children with chronic infection by *P. aeruginosa* and uncolonized children [30].

A study on estimating body composition and resting energy expenditure (REE) in children with CF did not reveal any differences in the mean values for basic anthropometric parameters between colonized and uncolonized children [31]. These authors carried out an additional examination of body composition using dual-energy X-ray absorptiometry, which showed that chronic infection caused a marked drop in lean body mass (LBM) that could not be detected by analyzing indicators based on weight and height measurements.

In a study from Chile, on the other hand, REE and body composition in children with CF with a stable clinical picture without chronic respiratory infection was comparable to that in healthy children [32]. This is consistent with the results of the present study, in which the least disturbance of growth and nutritional status during the course of the disease was found in uncolonized children.

Severe malnutrition is associated with an approximately 50% increase in basal metabolism when individuals with CF suffer from respiratory tract infections as compared to affected individuals who were free from infection. When chronic infection is present, there is also an increase in muscle protein catabolism, a decrease in protein synthesis,

inadequate oral intake, and a severe alteration in digestion, which causes a reduction in lean body mass, especially in the extremities [31, 33]. When chronic infection of the respiratory tract by *P. aeruginosa* is present, the energy cost of maintaining life processes increases to the point that there is not enough energy left over for normal childhood development.

The authors concluded that the present study on a population of children and young people with CF indicates that somatic development is greatly disordered in children with CF as compared to development in healthy children. The results show that, in the children examined, nutritional status is more adversely affected than growth.

Of the factors related to the clinical picture of the disease, only the presence of respiratory tract colonization by *P. aeruginosa* had an effect on physical development in the children examined. Neither the type of mutation present nor age at diagnosis had any significant effect. Chronic colonization interfered with growth and markedly worsened nutritional status, and was also associated with reductions in both total and lean body mass. Early nutritional intervention can improve nutritional state and pulmonary function in children with CF.

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