Original article

Arm muscle area for the longitudinal assessment of nutritional status in paediatric patients with cystic fibrosis - A single centre experience

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**A B S T R A C T**

**Background:** In cystic fibrosis, adequate nutrition contributes to good long-term prognosis. A body mass index (BMI) at or above the 50th percentile for age and sex in all children has been recommended. As researchers have described a depletion of fat-free mass despite normal BMI, longitudinal studies using more sensitive nutritional parameters are warranted. We evaluated anthropometric measurements in an attempt to identify early indicators of deteriorating nutritional status in our paediatric cohort.

**Methods:** We analysed datasets from children and adolescents between 2 and 179 years with at least two entries for triceps skinfold thickness and upper arm circumference in our patient database between January 1995 and December 2018. Arm muscle area (AMA) was calculated, and all values were expressed as z-scores from CDC growth charts.

**Results:** A total of 4,862 encounters from 161 paediatric patients (78 girls) were available, representing a median number of 28 visits during a median follow-up of 8.1 years per patient. Linear mixed effects models revealed relatively stable courses for weight, height, BMI and skinfold thickness up to adulthood. AMA was the only parameter which declined slightly ($r = -0.036$), particularly in boys. Kaplan-Meier analyses showed that AMA was the earliest parameter to decrease below -1 z-score between 6 and 18 years.

**Conclusions:** The present data suggest that compared with weight or BMI, AMA could serve as an earlier indicator of a deteriorating nutritional status. The benefit of assessing skinfold thickness and arm circumference routinely and calculating AMA from these measurements should be evaluated in large, prospective, multi-centre studies.

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**Abbreviations**

AMA arm muscle area
BIA bioelectrical impedance analysis
BMI body mass index
CDC centres for disease control and prevention
CF cystic fibrosis
CFTR cystic fibrosis transmembrane regulator
DEXA dual energy x-ray absorptiometry
FEV$_1$ forced expiratory volume in one second
FFM fat-free mass
GAMM generalised additive mixed effects models
IQR interquartile range
TSF triceps skinfold

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1. Introduction

In the care of children with cystic fibrosis (CF), clinicians aim to ensure that their patients have healthy lungs and normal weight when they pass into adulthood. Preventing nutritional deficits is associated with improved growth and respiratory function and is likely to improve prognosis [1]. Accordingly, height and weight are closely monitored throughout childhood. From the age of 2 years, BMI should also be calculated, as stated in the European Standards of Care [2]. Children and adolescents with cystic fibrosis should achieve the 50th percentile for BMI.

Using BMI as the sole indicator of nutrition status can be misleading, when body composition is not taken into account. The body is composed of two main components, fat mass and fat-free...
mass (FFM). FFM contains the internal organs, bone, and muscle. Significant differences in body composition between patients with cystic fibrosis and healthy controls have been reported [3]. Fat-free mass correlates more strongly with respiratory muscle function than BMI [4]. A satisfactory BMI may conceal a reduced fat-free mass in patients with cystic fibrosis. Such a "hidden depletion" of fat-free mass was observed by previous authors [5,6].

The most widely used methods to determine fat-free mass are dual energy x-ray absorptiometry (DEXA) and bioelectrical impedance analysis (BIA). These require special equipment and extra time for both patients and health care providers. An alternative and easier method is the measurement of skinfold thicknesses and upper arm circumference as introduced by Lohman et al. in the 1980s [7]. These techniques have been used for decades to calculate fat mass and fat-free mass [8–10]. The accuracy of the respective prediction equations is however limited. We therefore preferred to use sequential raw measurements in individual patients to detect changes in nutritional status over time. Reference values for skinfold thickness and upper arm circumference are available for both adults and children from different countries and study cohorts [8]. Percentiles or z-scores allow the assessment of the individual patient’s status throughout childhood compared to normal values. However, relatively little information is available from patients with cystic fibrosis. Some authors have suggested to perform longitudinal studies to detect changes in nutritional status including measurements of body composition [3,11].

We introduced skinfold measurements at our centre in 1995 and have since documented all values in our patient database. The present study examined the longitudinal development of anthropometric measurements and FEV₁ in our paediatric cohort between the ages of 2 and 17.5 years. The analysis included data obtained prior to the widespread introduction of CFTR modulators. We aimed to find parameters which are early indicators of a deteriorating nutritional status compared to the "classical" values weight, height, and body mass index.

2. Methods

2.1. Patient cohort

The CF Centre Innsbruck established a patient database in 1995, which contains parameters from all outpatient visits and from selected inpatient encounters. In addition to routine disease monitoring, skinfold thickness and upper arm circumference (UAC) were measured during regular outpatient visits since 1995. The present analysis evaluates paediatric patients aged 2.0 to 17.9 years who had at least two entries for anthropometric measurements between January 1, 1995 and December 31, 2018 (there were no patients with less than two measurements).

2.2. Measurements and reference values

Standard procedures[12] were used to determine body weight (in kg) and height (in cm), and body mass index (in kg/m²) was calculated as BMI = Weight ÷ (Height)² (in kg/m²). Triceps skinfold thickness (TSF), subscapular skinfold thickness and upper arm circumference (UAC) were measured in mm as recommended by Lohman et al. 7 by two highly trained nurses using a Harpenden caliper and Gulick II non-stretch, pliable tape. Arm muscle area (AMA) was calculated from TSF and UAC using the formula AMA = (UAC – π ·TSF²) ÷ 4π. Spirometry was performed according to Quanjer et al., and forced expiratory volume in one second (FEV₁) was assessed using the latest Global Lung Initiative reference values[13].

Height, weight, and body mass index were expressed in z-scores which were calculated using the appropriate growth charts established by the Centres for Disease Control and Prevention (CDC) [14]. Reference values by Addo and Himes were used for triceps skinfold [15] and upper arm circumference [16]. These reference values were calculated with the same populations that form the basis of the CDC growth charts. Z-scores were calculated using the respective LMS coefficients provided by Addo et al. After we noticed some discrepancies regarding arm muscle area in adolescent girls, we corresponded directly with the author who kindly provided us with revised reference values.

2.3. Statistics

Linear mixed effects models were fitted separately by sex for each anthropometric parameter with age as a covariate. All models included a random intercept and random slope per patient to account for interdependence of measurements within each patient. We did not adjust the models for disease severity. For the mixed models, p-values were estimated using Wald-Tests and the conditional R squared was reported as described by Nakagawa et al. [17]. Additionally, Generalised Additive Mixed Effects Models (GAMM) were fitted for visual comparison of the longitudinal development of parameters by modelling the parameter as a regression spline function of age. Kaplan-Meier curves were estimated for each anthropometric parameter in boys and girls aged 6 who had normal z-scores --1 for each parameter, and an event was defined as a drop in z-score below -1 for two consecutive measurements. The age of 6 years was chosen because the analysis should start at an age when most children of our cohort still had a relatively normal nutritional status. All models were estimated separately for girls and boys. The statistical analysis was performed with R 4.0.2[18].

Ethics approval was obtained from the ethics committee at Medical University of Innsbruck (UN5050S/324/4.10). Written informed consent was obtained from all patients and their legal representatives.

3. Results

3.1. Patient characteristics

Between January 1995 and December 2018, the database at the CF Centre Innsbruck contained 4862 encounters from 161 paediatric patients (78 girls) aged 2 to 17.9 years who had at least two entries for skinfold measurements. A median (IQR) of 28 (14–45) visits per patient were made during a median follow-up of 8.1 years per patient. The diagnosis of cystic fibrosis was made at a median (IQR) age of 52 (36–157) days. Newborn screening was performed in 92 infants.

Patient characteristics for the whole group across all calendar years and encounters are depicted in Table 1. In addition, the results at the last entry of each patient are presented, i.e. at a median age of 17.5 years. At that time point, 12 patients had CF related diabetes, and 8 received oral corticosteroids.

3.2. Nutritional status throughout childhood and adolescence

Fig. 1 illustrates the longitudinal course of BMI and AMA in children and adolescents. Patients of both sexes showed increasing z-scores for BMI and triceps skinfold between 2 and 8 years of age, with median z-scores approaching zero in 8-year-old boys. During adolescence, boys showed a decline in BMI and AMA, while no deterioration was seen in girls, who had started at a lower level. At age 18, the median z-scores for AMA were lower than BMI z-scores in both girls and boys. The spline curves display changes during childhood in more detail than simple linear regression lines.

Legend to Fig. 1. Z-scores for body mass index (BMI, left) and arm muscle area (AMA, right) in n = 83 boys (blue) and n = 78
Table 1
Clinical characteristics of N = 161 patients during 4862 patient encounters between 1995 and 2018 and at the last entry for each patient.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median [Inter-quartile range]</th>
<th>Data from all patient encounters (N = 4862)</th>
<th>Median [Inter-quartile range]</th>
<th>Data at the last entry for each patient (N = 161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>10.1 [6.4; 13.8]</td>
<td>17.5 [11.4; 17.8]</td>
<td>50.6 [36.9; 60.5]</td>
<td></td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>30.8 [20.7; 45.5]</td>
<td>161.3 [148.2; 170.5]</td>
<td>18.8 [16.9; 21]</td>
<td></td>
</tr>
<tr>
<td>Height [cm]</td>
<td>138.4 [117.5; 157.2]</td>
<td>87.9 [67.7; 97.8]</td>
<td>50.6 [36.9; 60.5]</td>
<td></td>
</tr>
<tr>
<td>Body Mass Index [kg/m²]</td>
<td>16.4 [15.0; 18.5]</td>
<td>87.9 [67.7; 97.8]</td>
<td>18.8 [16.9; 21]</td>
<td></td>
</tr>
<tr>
<td>Weight [z-score]</td>
<td>-0.25 [-0.88; 0.36]</td>
<td>-0.01 [-0.53; 0.59]</td>
<td>-0.23 [-0.83; 0.25]</td>
<td></td>
</tr>
<tr>
<td>Height [z-score]</td>
<td>-0.02 [-0.65; 0.61]</td>
<td>-0.01 [-0.53; 0.59]</td>
<td>-0.23 [-0.83; 0.25]</td>
<td></td>
</tr>
<tr>
<td>BMI [z-score]</td>
<td>-0.32 [-1.01; 0.24]</td>
<td>-0.27 [-0.99; 0.18]</td>
<td>-0.32 [-1.01; 0.24]</td>
<td></td>
</tr>
<tr>
<td>Triceps skinfold [z-score]</td>
<td>-0.28 [-0.89; 0.51]</td>
<td>-0.38 [-1.05; 0.28]</td>
<td>-0.28 [-0.89; 0.51]</td>
<td></td>
</tr>
<tr>
<td>Subscapular skinfold [z-score]</td>
<td>-0.11 [-0.65; 0.54]</td>
<td>-0.11 [-0.91; 0.44]</td>
<td>-0.11 [-0.91; 0.44]</td>
<td></td>
</tr>
<tr>
<td>Upper arm circumference [z-score]</td>
<td>-0.40 [-1.08; 0.27]</td>
<td>-0.43 [-1.23; 0.17]</td>
<td>-0.40 [-1.08; 0.27]</td>
<td></td>
</tr>
<tr>
<td>Arm muscle area [z-score]</td>
<td>-0.55 [-1.38; 0.32]</td>
<td>-0.52 [-1.54; 0.44]</td>
<td>-0.55 [-1.38; 0.32]</td>
<td></td>
</tr>
<tr>
<td>FEV₁ [% predicted]</td>
<td>92.4 [77; 103]</td>
<td>87.9 [67.7; 97.8]</td>
<td>92.4 [77; 103]</td>
<td></td>
</tr>
<tr>
<td>FEV₁ [z-score]</td>
<td>-0.64 [-1.91; 0.26]</td>
<td>-1.02 [-2.7; -0.19]</td>
<td>-0.64 [-1.91; 0.26]</td>
<td></td>
</tr>
<tr>
<td>P. aeruginosa positive at clinic visit [%]</td>
<td>14.4 [7.6; 22]</td>
<td>24.1 [7.6; 22]</td>
<td>14.4 [7.6; 22]</td>
<td></td>
</tr>
<tr>
<td>S. aureus positive at clinic visit [%]</td>
<td>32.4 [10.5; 63.4]</td>
<td>32.6 [10.5; 63.4]</td>
<td>32.4 [10.5; 63.4]</td>
<td></td>
</tr>
</tbody>
</table>

(a): N = 3875 observations; N = 143 patients  
(b): N = 4385 observations; N = 141 patients

Anthropometric data showed that arm muscle area and upper arm circumference had the lowest median z-scores of -0.55 and -0.40, respectively, while the median z-scores for BMI, weight and height were higher.

3.3. Early indicators of nutritional depletion

To identify which parameters decline particularly early, we investigated subgroups of 41 girls and 45 boys who had normal z-scores > -1 at age 6 for each of the seven parameters. Kaplan-Meier analyses were performed (Fig. 2) and an event was defined as the time when the z-score dropped to a value below -1 for two consecutive measurements. A 50% probability for a decrease to below -1 z-scores was reached for AMA between the ages 11 and 12 in boys, while none of the other five parameters reached the 50% probability level up to 17.9 years of age. In girls, AMA also was the earliest parameter to decline, whereas triceps skinfold decreased later. At the age of 18, less than 25% of patients remained at an AMA z-score above -1, while approximately 75% of adolescents still had a BMI z-score above -1.

Legend to Fig. 2: Analysis of subgroups of n = 45 boys (left) and n = 41 girls (right) who had normal results (> -1 z-score) for each of the seven nutritional parameters at age 6. The probability of the z-score falling below -1 was estimated, and an event was defined as a drop in z-score below -1 for two consecutive measurements.

3.4. Arm muscle area and lung disease

To relate nutritional status to the severity of lung disease, we generated two groups of data with the 50% best and 50% worst FEV₁ z-scores, i.e. either above or below the median. Boxplots for the AMA z-scores in these two groups are depicted in Fig. 3.

Legend to Fig. 3: Data are from patient encounters with the presence or absence of the respective criterion, resulting in two groups each. FEV₁ groups are from values above (grey) or below (red) the median. The CFTR groups are either F508del heterozygous (grey) or F508del homozygous (red). Bacterial colonisation groups are from encounters without (grey) or with (red) detection of either S. aureus or P. aeruginosa. The boxplots show the median, the 25th and the 75th percentiles for arm muscle area z-scores, with the whiskers ending at the 10th and the 90th percentiles, respectively. Please note that the assumption of independent readings might not always be fulfilled. For example, a patient could show up in both groups if the sputum is P. aeruginosa positive at one encounter but not at another visit.
Table 2
Change in nutritional parameters with increasing age: Linear mixed model analyses of 4862 patient encounters.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Boys (N = 83)</th>
<th></th>
<th>Girls (N = 78)</th>
<th></th>
<th>All children (N = 161)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>R²</td>
<td>β</td>
<td>R²</td>
<td>β</td>
<td>R²</td>
</tr>
<tr>
<td>Weight</td>
<td>-0.011</td>
<td>0.933</td>
<td>0.038**</td>
<td>0.911</td>
<td>0.014</td>
<td>0.923</td>
</tr>
<tr>
<td>Height</td>
<td>-0.015</td>
<td>0.958</td>
<td>0.014</td>
<td>0.950</td>
<td>0.001</td>
<td>0.954</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.007</td>
<td>0.884</td>
<td>0.050***</td>
<td>0.849</td>
<td>0.028</td>
<td>0.867</td>
</tr>
<tr>
<td>Triceps skinfold</td>
<td>0.010</td>
<td>0.377</td>
<td>0.026**</td>
<td>0.309</td>
<td>0.018**</td>
<td>0.349</td>
</tr>
<tr>
<td>Subscapular skinfold</td>
<td>0.012</td>
<td>0.703</td>
<td>0.036**</td>
<td>0.548</td>
<td>0.023**</td>
<td>0.631</td>
</tr>
<tr>
<td>Upper arm circumference</td>
<td>-0.026</td>
<td>0.892</td>
<td>0.042***</td>
<td>0.846</td>
<td>0.007</td>
<td>0.870</td>
</tr>
<tr>
<td>Arm muscle area</td>
<td>-0.074***</td>
<td>0.514</td>
<td>0.002</td>
<td>0.522</td>
<td>-0.036**</td>
<td>0.522</td>
</tr>
<tr>
<td>FEV₁</td>
<td>-0.063**</td>
<td>0.762</td>
<td>-0.096***</td>
<td>0.814</td>
<td>-0.079**</td>
<td>0.789</td>
</tr>
</tbody>
</table>

The mixed model analysis was performed with age as the independent variable and the different parameters as outcome variables. Nutritional parameters and FEV₁ are expressed as z-scores. β is the regression coefficient, explaining the direction and magnitude of change of each parameter with increasing age of the patient. For example, arm muscle area z-score decreased by 0.074 in boys per year, while body mass index showed no decline with age. R² is the coefficient of determination which denotes the proportion of the variation in the outcome variable which is predictable from the independent variable.

* *** significant at p < 0.001; ** significant at p < 0.01; * significant at p < 0.05. Note that p-values were not adjusted for multiple comparisons leading to an increase in type I error.

Fig. 2. Probability of declining anthropometric parameters between age 6 and 18.

Fig. 3. Arm muscle area z-score and severity of CF disease.
Table 3
Nutritional status and FEV\(_1\) during patient encounters in four different treatment periods between 1995 and 2018.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable (z score)</td>
<td>Median, IQR</td>
<td>Median, IQR</td>
<td>Median, IQR</td>
<td>Median, IQR</td>
</tr>
<tr>
<td>Height</td>
<td>-0.38 [-1.18; 0.34]</td>
<td>-0.15 [-0.63; 0.52]</td>
<td>0.13 [-0.53; 0.67]</td>
<td>0.16 [-0.44; 0.87]</td>
</tr>
<tr>
<td>Weight</td>
<td>-0.57 [-1.43; 0.12]</td>
<td>-0.35 [-0.97; 0.28]</td>
<td>-0.17 [-0.75; 0.43]</td>
<td>-0.04 [-0.59; 0.50]</td>
</tr>
<tr>
<td>Body mass index</td>
<td>-0.48 [-1.46; 0.15]</td>
<td>-0.36 [-1.16; 0.18]</td>
<td>-0.32 [-0.88; 0.26]</td>
<td>-0.15 [-0.77; 0.35]</td>
</tr>
<tr>
<td>Triceps skinfold thickness</td>
<td>-0.37 [-0.90; 0.17]</td>
<td>-0.41 [-0.97; 0.19]</td>
<td>-0.10 [-0.74; 0.70]</td>
<td>-0.17 [-0.92; 1.50]</td>
</tr>
<tr>
<td>Subscap. skinfold thickness</td>
<td>-0.38 [-0.91; 0.19]</td>
<td>-0.12 [-0.61; 0.35]</td>
<td>-0.06 [-0.62; 0.68]</td>
<td>0.12 [-0.53; 0.80]</td>
</tr>
<tr>
<td>Upper arm circumference</td>
<td>-0.81 [-1.59; -0.06]</td>
<td>-0.57 [-1.13; 0.02]</td>
<td>-0.40 [-1.07; 0.29]</td>
<td>-0.02 [-0.61; 0.55]</td>
</tr>
<tr>
<td>Arm muscle area</td>
<td>-0.82 [-1.59; -0.01]</td>
<td>-0.49 [-1.18; 0.16]</td>
<td>-0.63 [-1.31; 0.23]</td>
<td>-0.20 [-1.56; 0.74]</td>
</tr>
<tr>
<td>FEV(_1)</td>
<td>-1.34 [-2.46; -0.37]</td>
<td>-0.73 [-1.98; 0.26]</td>
<td>-0.46 [-1.75; 0.48]</td>
<td>-0.33 [-1.38; 0.36]</td>
</tr>
</tbody>
</table>

The table shows the median (IQR) z-scores of all patient visits during the respective period. For example, the median FEV\(_1\) z-score was -1.34 in the first period between 1995 and 2000, and it increased to -0.33 between 2013 and 2018. In the most recent period, patients had much more normal nutritional status and FEV\(_1\) than in earlier years. Arm muscle area and triceps skinfold thickness were the parameters with the most strongly negative z-scores.

The median AMA z-score of -0.2 was completely normal in patients with better FEV\(_1\), in contrast to children with worse lung function. We also analysed patient encounters with or without pathogenic bacteria (P. aeruginosa or S. aureus) in specimens from sputum or throat swabs. While P. aeruginosa infection was associated with lower AMA z-scores, there were no pronounced differences in the groups with or without S. aureus colonisation. Regarding the CFT mutation, F508del heterozygous patients did not substantially differ from F508 homozygous patients with respect to median AMA z-score, but the interquartile range had a higher upper limit in heterozygous patients.

3.5. Longitudinal development from 1995 to 2018

To detect possible changes over 24 years of CF care at our centre, we created four treatment periods of six years each and calculated medians and interquartile ranges (IQR) of nutritional parameters and FEV\(_1\) for each period (Table 3). Nearly all parameters showed the highest median z-scores during the most recent period and the lowest values between 1995 and 2000. FEV\(_1\) showed the biggest improvement, with a median increase of almost 1 z-score over 24 years. During the most recent 6-year period, all median z-scores were between -033 (FEV\(_1\)) and +0.16 (weight), indicating that many patients had nearly normal nutritional status and preserved lung function. Notably, the pattern of arm muscle area or upper arm circumference being the most abnormal anthropometric parameters was observed in each of the four treatment periods.

4. Discussion

In the present study, the nutritional status of children and adolescents with cystic fibrosis, analysed longitudinally in a single centre over 24 years, remained within the normal range in the majority of patients. Routine measurements of skinfold thickness and arm circumference provided supplementary information in addition to weight and height, suggesting that arm muscle area declined earlier in the course of the disease and to a larger degree than body mass index or other parameters. The use of sensitive indicators of nutritional deterioration enables clinicians to intervene early and to promptly intensify treatment with the aim of maintaining the best nutritional status for as long as possible.

4.1. Body mass index in cystic fibrosis registries

In the 1990s, when our patient database was established, subjects with cystic fibrosis were smaller and lighter than healthy children, and they experienced a considerable decline of clinical status between childhood and adulthood [19,20]. Nowadays the situation is much better due to improvements in monitoring and treatment. In 2018, the median BMI in young children aged 2 to 3 years was at the 40th percentile as reported in the German CF registry, with only a slight decrease in values up to late adolescence [21]. In the US, the median BMI percentile of patients aged 2 to 19 years was 58.4 in the same year [22]. The BMI results are difficult to compare, however [23], since the German registry uses the latest national reference values [10] rather than the older CDC growth charts form the US [14].

While national patient registries report cross-sectional data from a single calendar year, we analysed the longitudinal development of parameters by fitting generalised additive mixed effects models. The regression spline functions showed satisfactory BMI values in young children, with only a slight decline after age 10 in male, but not in female adolescents. During the most recent period up to 2018, the median BMI z-score was -0.12, representing an increase of +0.33 z-scores compared to 1995 to 2000. Thus, BMI improved considerably with time, just as described in the US patient registry for different birth cohorts.

4.2. Body composition assessments

In addition to the essential parameters weight and height, researchers have looked at more sophisticated aspects of nutrition. Body composition has been determined by assessing its two major compartments body fat and fat-free mass. Different methods have been used in CF cohorts to evaluate fat free mass, predominantly DXA and BIA [24,25]. Recent cross-sectional studies have reported decreased fat-free mass in both children and adults with CF [5]. The median FFM z-scores measured by BIA were -1 in a group of French children [25] and -1.1 in Dutch CF patients between 4 and 18 years of age [11]. However, many patients with subnormal fat-free mass had BMI values within the normal range. Thus, this “hidden depletion of fat-free mass” was undetectable if only weight, height and BMI were used as indicators for malnutrition [5].

In the present study, we analysed triceps and skinfold thicknesses and upper arm circumference measurements, which had been collected prospectively routine patient encounters. While we did not determine fat-free mass, we regarded triceps skinfold thickness as a surrogate to body fat, and arm muscle circumference and arm muscle area as surrogate parameters for fat-free mass. During outpatient visits, skinfold thicknesses and arm circumference were part of the assessment. If any of these values deteriorated, this was interpreted as a warning sign and resulted in consulting the dietician.

When measurements of skinfold thickness are used for routine outpatient care, it is important to employ standardised procedures to minimise inter- and intraobserver variability. Adequate training of new staff and regular quality control checks are necessary to ensure reliable measurements.
In our cohort, arm muscle area had the lowest median z-score of -0.55 of all nutritional parameters observed, while BMI, weight, height, and skinfold thickness were substantially better. When comparing anthropometry and BIA, authors from the Netherlands reported reductions of both fat-free mass determined by BIA and upper arm circumference, with similar mean z-scores of about -1 for both parameters [11]. The mean BMI z-score of -0.13 was however close to normal in the same patients. Thus, the long-term observations of the present study, i.e. decline in arm muscle area suggesting a depletion of fat-free mass despite satisfactory BMI, are consistent with cross-sectional and short-term longitudinal data from the literature.

4.3. Fat-free mass and clinical characteristics

Fat-free mass is associated with lung function in children with CF. In a cross-sectional study, a decrease in FFM z-score of 1 unit was associated with a decrease in FEV1 by 9.3%, and the authors suggested that diaphragmatic function was related to muscle mass [25]. A recent narrative review recommended to assess body composition in conjunction with BMI, since the detection of FFM loss predicts an imminent decline of pulmonary function [5]. In our patients, arm muscle area z-score was higher larger in the group with FEV1 values above the median than in patients below the median. Furthermore, z-scores for arm muscle area were lower at encounters with P. aeruginosa detection than at clinic visits with P. aeruginosa negative specimens. A weak association between P. aeruginosa infection and fat-free mass depletion was also shown by Charatsi et al. who reported that 6 out of 9 patients with fat-free mass depletion were infected with P. aeruginosa in contrast to only 10 of 31 patients with normal fat-free mass [25]. Regarding the F508del CFTR mutation, we found no relevant differences in arm muscle area between homozygous and heterozygous patients.

4.4. Longitudinal results

Regarding the longitudinal development of nutrition and lung function in our patients, the regression coefficients for six of the seven nutritional parameters were around zero in our patient cohort, indicating a stable situation appropriate for age. Only upper arm muscle area declined significantly at a rate of -0.036 z-scores per year, suggesting that muscle gain was somewhat smaller than expected in healthy children. This occurred despite the fact that a sports therapist is part of the multiprofessional team and works out individual training plans with the patients. In addition, all caregivers encourage the children to perform regular physical activity.

Only few longitudinal studies on body composition parameters have been published in subjects with CF. Zemel et al. [26] described declines in weight and triceps skinfold thickness of -0.09 and -0.15 z-scores per year, respectively, in boys who were measured repeatedly over three years. In another three-year study, Stettler et al. [27] reported lower gains of fat-free mass in CF individuals compared to healthy children. UK researchers stated that fat and fat-free mass were lower in CF patients of both sexes compared to controls, and that z-scores for height, weight and BMI decreased with age [28].

4.5. Detecting early changes in nutrition

By comparing the long-term development of several parameters, we aimed to identify early predictors of an adverse clinical course. In a Kaplan-Meyer-analysis of the 86 children with normal parameters above -1 z-score at age 6, we evaluated the time point when the z-score declined to below -1. Arm muscle area was the first value which decreased significantly, much earlier than body mass index, weight or height. Up to age 12, arm muscle area had dropped below -1 z-scores in more than half of boys and girls.

4.6. Strengths and weaknesses

The present dataset from a single centre contains 4862 patient encounters during a period of 24 years. To our knowledge, this is the first longitudinal evaluation on skinfold measurements in CF with such a long observation time. We started the analysis in 1995, after routine IRT newborn screening had been established in Innsbruck, resulting in early diagnosis of infants with CF, and we finished the evaluation in 2018, at a time when only a few patients had received CFTR modulator therapy. We evaluated a median of 28 visits per patient during a median of 8.1 years, while previous authors reported only up to 3 years of longitudinal follow-up. In addition to conventional parameters such as weight, height, and body mass index, we performed skinfold thickness and arm circumference measurements, in an attempt to find surrogate markers for fat-free mass. To simplify comparisons between paediatric patients of different age, we calculated z-scores for all parameters, using reference values which were derived from the same CDC cohort of children and adolescents. The prospective collection of relevant disease parameters in our local patient registry allowed relation of nutritional parameters to clinical data. Finally, the CF Centre at the University of Innsbruck introduced a quality management system in 2006, with bi-annual certificates according to ISO 9001:2015. This is why processes are highly standardised and described in standard operating procedures, facilitating a relatively homogenous approach over many years.

Some weaknesses must however be addressed. First, a single center analysis precludes the results from being generalised to other CF populations. Second, we neither determined body composition with widely accepted methods like BIA or DEXA, nor did we calculate fat-free mass using four different skinfolds [29]. These more elaborate techniques would considerably prolong patient encounters and would require a setting similar to clinical trials. By contrast, measuring triceps skinfold thickness and arm circumference were easy to perform during patient encounters and only took a few minutes.

5. Conclusions

An analysis of height, weight, and body mass index over the last 24 years revealed that most children at our centre had a satisfactory nutritional status up to adulthood. Results from the most recent period up to 2018 were better than those from earlier years. When comparing different nutritional parameters in the pre-modulator era, arm muscle area, calculated from measurements of triceps skinfold thickness and upper arm circumference, had the lowest z-scores of all items. Furthermore, arm muscle area declined in many patients from the age of 6, whilst other parameters remained relatively stable. These data suggest that arm muscle area could serve as an early indicator of a deteriorating nutritional status. The benefit of measuring skinfold thickness and arm circumference during routine patient care should be evaluated in large, prospective, multi-centre studies.

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Declaration of Competing Interest

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Credit authorship contribution statement

Helmut Ellemunter: Conceptualization, Investigation, Validation, Supervision, Resources, Writing – review & editing. Markus Dumke: Formal analysis, Data curation, Visualization. Gratiana Steinkamp: Conceptualization, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing.

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