Comparison of total body chlorine, potassium, and water measurements in children with cystic fibrosis1–3

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ABSTRACT

Background: Symptoms of cystic fibrosis (CF) may limit the utility of total body chlorine (TBCl) and total body potassium (TBK) measurements for assessing body fluid compartments of children.

Objective: This study assessed relations among independent measurements of TBCl, TBK, and total body water (TBW) in children with CF.

Design: We compared cross-sectional measurements of TBCl by in vivo neutron activation analysis, TBK by whole-body counting of 40K, TBW by D2O dilution [TBW(D2O)], and TBW from TBCl and TBK [TBW(Cl + K)] in 19 prepubertal children (13 boys) aged 7.6–12.5 y who had mild symptoms of CF. Body-composition measurements were compared with data from previous studies of healthy children.

Results: Subjects with CF had deficits in TBCl, TBK, TBW, and body weight compared with control reference data (P < 0.05). The ratios (TBCl + TBK)/TBW and TBK/TBW were not significantly different from control reference values, and plasma chloride and potassium concentrations were within control reference ranges. The sum of TBCl and TBK correlated with TBW(D2O) (r2 = 0.79, P < 0.001), and TBK(TCl + K) correlated with TBW(D2O) (r2 = 0.78, P < 0.001). TBW(TCl + K) was similar to TBW(D2O) (3 ± SEM: 19.0 ± 0.5 compared with 19.4 ± 0.5 L; NS).

Conclusions: Prepubertal children with mild symptoms of CF can develop deficits in TBCl, TBK, and TBW that reflect chronic energy malnutrition. Mild symptoms of CF do not appear to affect normal relations among TBCl, TBK, and TBW. Measurements of TBCl and TBK may be used to assess body fluid compartments in these patients. Am J Clin Nutr 2000;71:36–43.

KEY WORDS Body composition, total body chlorine, total body potassium, total body water, extracellular water, intracellular water, cystic fibrosis, prepubertal children

INTRODUCTION

Protein-energy malnutrition is a common sequela in children with cystic fibrosis (CF) (1) and may result in abnormal whole-body distributions of electrolytes and fluids (2–4). The assessment of whole-body electrolyte and fluid compartments is therefore important in determining the nutritional status of children with CF.

Measurements of total body chlorine (TBCl) and total body potassium (TBK) have been used to derive estimates of extracellular and intracellular fluid compartments in normal-weight and obese adults (5, 6). This approach is based on the assumptions that ≈88% of TBCl is found in extracellular water (ECW) (7) and that >96% of TBK is found in intracellular water (ICW) (8).

In children with CF, TBCl and TBK measurements may be influenced by factors that include protein-energy malnutrition and the transepithelial chloride transport abnormality that is the intrinsic defect in CF (9). Although TBCl, TBK, and fluid compartments were studied previously in children with CF (2–4, 10–12, and IRJ Humphries and KJ Gaskin, unpublished observations, 1996), interpretation of these data is problematic because of the small numbers of subjects, wide variations in disease severity, incomplete reporting of disease symptoms and body components, and use of body-composition methods that may be invalid in CF populations.

The aim of this study was to define body composition in a group of clinically stable prepubertal children with mild symptoms of CF by 1) comparing independent measurements of TBCl, TBK, and total body water (TBW) and 2) investigating the respective relations of TBCl and TBK to ECW and ICW.

SUBJECTS AND METHODS

Subject selection

The study group consisted of 19 children (13 boys) with CF who were aged 7.6–12.5 y. All subjects were selected from the CF clinic of the Royal Children's Hospital, Melbourne, according to the following criteria: 1) age 7.0–13.0 y; 2) prepubertal (ie, Tanner stages 1 or 2); 3) positive diagnosis of CF on the basis of genotyping or pulmonary and gastrointestinal symptoms complemented by increased sweat chloride concentrations; 4) mild...
symptoms of lung disease as judged by a physical examination, chest X-rays, and spirometry tests; 5) no pulmonary exacerbations that required hospitalization within 2 mo of the study; 6) no hospitalization within 2 mo of the study; 7) weight change <1.5 kg over the 2 mo before the study; 8) no comorbidities likely to confound body-composition measurements (eg, clinical or biochemical evidence of liver disease or hepatosplenomegaly, pancreatitis, diabetes, or edema); and 9) no history of long-term (>1 y) use of medications likely to confound body-composition measurements (eg, corticosteroids, growth hormone, or diuretics). Reference data from previous studies of healthy children were used to interpret clinical, biochemical, and body-composition measures.

Study protocol
All subjects were studied as outpatients in 2 phases with the approval of the human ethics committees of both the Royal Children’s Hospital and the Monash Medical Centre and the signed, witnessed, and informed consent of subjects and their parents or guardians. In phase 1, clinical status, diet, and pancreatic function were assessed. In phase 2, anthropometry, body composition, and plasma biochemistry were assessed within a 4-h morning session. Each subject participated in both phases within a period of ≤12 wk.

Clinical assessment
Body weight was measured with a digital scale and body height was determined by using a stadiometer according to the standards of Lohman et al (13). Anthropometric measures were interpreted by using World Health Organization (WHO) normal population percentiles for weight and height (14). Growth velocities were expressed as a percentage of the normal 50th-percentile growth velocities reported by Tanner et al (15), and pubertal status was determined according to the Tanner stages of development (16).

Medical records of spirometry test results were reviewed to determine each subject’s measure of forced expiratory volume in 1 s (FEV1), expressed as a percentage of that expected of healthy children of the same age and sex. The pulmonary status of each subject was assessed by a thoracic physician and assigned a Holzer score (17) as follows: 0 (no lung disease) for subjects with no persistent cough, no sputum production, a normal chest radiograph, and an FEV1 > 80%; 1 (minimal lung disease) for subjects with persistent cough, no sputum production, a chest radiograph showing minimal streaking, and an FEV1 > 60% but <80%; and 2 (mild lung disease) for subjects with persistent cough, sputum production <10 mL/d, a chest radiograph showing bronchial-wall thickening and minimal hyperinflation, and an FEV1 > 65% but <85%.

Subjects receiving pancreatic enzymes at the time of the study were irradiated unilaterally by a 0.2-GBq 252Cf neutron source from shoulder to midthigh in both supine and prone positions. Prompt gamma-ray spectra were measured with 2 pairs of NaI(Tl) crystals (each crystal: 10 × 10 × 15 cm) positioned on both sides of the subject. TBCl was estimated from the ratio of chlorine-to-hydrogen counts as determined from the measurement of 8.57 and 2.22 MeV prompt gamma-rays from the respective reactions 35Cl(n,γ)36Cl and 1H(n,γ)D. The chlorine-to-hydrogen count ratio was corrected for the effect of body width and thickness on background and gamma-ray attenuation. Total body hydrogen was used as an internal standard, which was determined by using a 4-compartment model of body weight (22). The total exposure time per measurement scan was 630 s and the effective dose equivalent for a small child was 0.25 mSv (Q = 20, indicating exposure to neutrons). During this study, the assay error and precision were determined to be approximately 3% and 10% (CV), respectively, for TBCl measurements.

TBK was measured by counting 1.46 MeV gamma-ray emissions from 40K by using a shadow shield counter (23). Subjects rested supine on a moveable bed that passed through a symmetric array of four 40 × 10 × 10-cm NaI(Tl) detectors shielded within an enclosed, box-like steel chamber; the total scan time was 30 min. Measurements were calibrated against a potassium-rich, child-size box phantom, and a correction factor was applied to account for the effect of body thickness and width on gamma-ray attenuation (21). During this study, the error and precision of TBK measurements were determined to be approximately 2.5% and 4% (CV), respectively.

TBW was measured by using the D2O isotope dilution method (24). A baseline venous blood sample was first collected from the fasting subject and then an oral dose of 0.4 g 99.9% pure D2O/kg body wt was administered with a mouthwash of deionized water (100 mL). The subject fasted for a further 2–3-h equilibration period until a second venous blood sample was collected. The D2O plasma concentration of each plasma sample was determined in triplicate by using the Fourier transform infrared analysis technique and the average measure was then used to determine TBW by using the equation

\[
TBW(D2O)(L) = \frac{D2O\ dose\ (g)}{[(C2 - C1) \times 0.94 \times 0.95]}\]

(1)

where C1 is the plasma concentration of D2O at baseline, C2 is the D2O plasma concentration after the equilibration period, 0.94 is a factor that corrects for the protein content of plasma, and 0.95 is a factor that corrects for the fraction of 1H that exchanges with nonaqueous 2H. The assay measurement error and precision for determining D2O concentrations in spiked standard solutions were reported to be approximately 1% and 2% (CV), respectively (25).
Reference values for the ratios (TBCl + TBK)/TBW and TBCl/TBK were determined from the data of Cheek (26). Selected reference constants were representative of healthy children aged 10 y. Measurements of TBCl, TBK, and TBW were compared with predictor equations derived from data reported by previous studies of healthy children (26–32). The predictor equations used were as follows:

\[
\begin{align*}
\text{TBCl (g)} &= 0.380 \times \text{age}^2 - 3.416 \times \text{age} + 38.23 & (2) (26-29) \\
\text{TBCl (g)} &= 0.00806 \times \text{height}^2 - 1.528 \times \text{height} + 99.44 & (3) (26-29) \\
\text{TBK (g)} &= 0.721 \times \text{age}^2 - 6.973 \times \text{age} + 66.940 & (4) (29) \\
\text{TBK (g)} &= 0.0156 \times \text{height}^2 - 3.071 \times \text{height} + 195.8 & (5) (29) \\
\text{TBW (L)} &= 1.986 \times \text{age} + 0.046 & (6) (30-32) \\
\text{TBW (L)} &= 0.335 \times \text{height} - 26.089 & (7) (30-32)
\end{align*}
\]

where age is in years, height is in centimeters, and sex was found to be a nonsignificant predictor of TBCl, TBK, and TBW. The appropriateness of these equations is in part supported by the following criteria used to select the population reference data: 1) only whites were included; 2) only prepubertal children were included unless puberty per se did not significantly affect body composition; 3) the weight and height of selected populations were representative of the WHO 50th-percentile values for weight-for-age, weight-for-height, and height-for-age (14); 4) selected populations were assessed by body-composition methods similar to those used in this study; and 5) selected population reference data allowed for comparisons on a sex-, age-, and height-standardized basis. Measurements of TBCl, TBK, and TBW were expressed as a percentage of the expected reference value for age or for height as determined by the aforementioned predictor equations.

ECW was derived from the measurement of TBCl as

\[
\text{ECW (L)} = \left[ \frac{\text{TBCl (mmol)} \times 0.88 \times 0.95 \times 0.94}{[\text{Cl}]_p (mmol/L)} \right]
\]

where 0.88 is the assumed proportion of TBCl found in ECW, 0.95 accounts for the Donnan equilibrium factor, 0.94 accounts for the protein content of plasma, [Cl]_p is the plasma chloride concentration measured in each subject, and [Cl]_p is assumed to be representative of the average chloride concentration of ECW (3, 7, 8). ICW was derived from the measurement of TBK as

\[
\text{ICW (L)} = \text{TBK (mmol)} \times (0.00833 \text{ kg/mmol}) \times 0.75 \text{ (L/kg)}
\]

where 0.00833 kg/mmol is the ratio of body cell mass to TBK and 0.75 is the ICW content of the body cell mass (33, 34). This equation assumes that 100% of TBK is found within the body cell mass.

TBW was also derived from measurements of TBCl and TBK as

\[
\text{TBW(Cl + K) (L)} = \text{ECW (L)} + \text{ICW (L)}
\]

Statistical analysis

The one-sample t test was used to compare standardized measures of body composition, growth, pulmonary and gastrointestinal status, and dietary intake with the hypothesized control value of 100%. Measurements of weight, height, and body mass index (BMI) were compared with population reference data published by the WHO on the basis of z scores (14). For individual subjects, the normal reference range of z scores was interpreted as $-2$ to $+2$. The one-sample t test was used to compare the subjects’ z scores with the hypothesized control z score of 0.

The Bland and Altman method of assessing agreement between 2 clinical methods (35) was used to compare TBW measurements determined by D$_2$O dilution with TBW measurements derived from the sum of TBCl and TBK. The paired t test was also used to compare absolute estimates of TBW(D$_2$O) with TBW(Cl + K).

Univariate linear regression analysis was used to assess relations between $I$) TBW(D$_2$O) and both TBW(Cl + K) and TBCl + TBK, 2) continuous clinical variables and the measurement bias between TBW(D$_2$O) and TBW(Cl + K), and 3) continuous clinical and laboratory variables on the one hand and body-composition variables on the other (GRAPHPAD PRISM, version 1.0; GraphPad Software, Inc, San Diego).

The unpaired t test was used to compare 2 subgroups of subjects (eg, boys compared with girls), and one-way analysis of variance with a Bonferroni correction was used to compare more than 2 subgroups of subjects (eg, genotype: F508/F508 compared with F508/other compared with other/other) (GRAPHPAD PRISM, version 1.0). An effect was assumed to be significant if $P < 0.05$.

RESULTS

Clinical assessment

Given that there were no significant sex differences in any of the clinical measures investigated, the clinical characteristics of boys and girls are combined in Table 1. The CF group had subnormal z scores for weight-for-age, weight-for-height, and BMI and a mean height z score indicative of a nonsignificant degree of stunting. Negative linear correlations were observed between age and z scores for weight-for-age ($r^2 = 32.2$, $P = 0.01$) and height-for-age ($r^2 = 37.0$, $P < 0.01$). Individual z scores for weight-for-age, weight-for-height, and height-for-age all fell within 2 SDs of reference medians. BMI-for-age z scores of all but 2 subjects fell within 2 SDs of the reference median.

Subjects showed a subnormal rate of growth in weight and a normal rate of growth in height. All subjects were prepubertal with Tanner scores of 1 or 2. Subjects had minimal symptoms of lung disease, as judged by a mean ($\pm$SEM) Holzer score of 0.9 $\pm$ 0.2, and subnormal lung function (FEV1 < 100%; $P < 0.001$). At the individual level, 6 subjects (all boys) showed no clinically overt symptoms of lung disease, 9 (5 boys) showed minimal symptoms of lung disease, and 4 (2 boys) showed mild symptoms of lung disease.

All subjects were pancreatic insufficient and used pancreatic-enzyme supplements. Dietary fat absorption tests were successfully completed for 15 of 19 subjects. These 15 subjects could absorb only 86.4% of ingested dietary fat with the use of pancreatic-enzyme supplements. Dietary fat absorption tests were successfully completed for 15 of 19 subjects. These 15 subjects could absorb only 86.4% of ingested dietary fat with the use of enzyme supplements.

At the time of study, all subjects were consuming an ad libitum diet. The 3-d weighed-food diary was completed by 18 of 19 subjects. A comparison with RDIs showed a significant deficit in total energy intake and a significant surplus of protein intake. Only 2 subjects (1 boy) reported taking salt-tablet supplements in quantities of about 1000 mg/d over the 3-d period of dietary assessment.
TABLE 1
Clinical and laboratory assessment of children with cystic fibrosis1

<table>
<thead>
<tr>
<th>Variable (n)</th>
<th>Clinical or laboratory assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) (n = 19, 13 boys)</td>
<td>10.4 ± 0.4 (7.6–12.5)</td>
</tr>
<tr>
<td>Anthropometry (n = 19, 13 boys)</td>
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</tr>
<tr>
<td>Weight z score</td>
<td>−0.52 ± 0.20 (−1.48–1.88)</td>
</tr>
<tr>
<td>Height z score</td>
<td>−0.20 ± 0.21 (−1.41–1.87)</td>
</tr>
<tr>
<td>Weight-for-height z score</td>
<td>−0.61 ± 0.17 (−1.74–0.72)</td>
</tr>
<tr>
<td>BMI z score</td>
<td>−0.67 ± 0.25 (−2.02–2.64)</td>
</tr>
<tr>
<td>Growth (n = 19, 13 boys)</td>
<td></td>
</tr>
<tr>
<td>Weight velocity (% of ideal)</td>
<td>70 ± 7 (21–159)</td>
</tr>
<tr>
<td>Height velocity (% of ideal)</td>
<td>100 ± 4 (66–143)</td>
</tr>
<tr>
<td>Pubertal status (Tanner stage)</td>
<td>1.1 ± 0.1 (1–2)</td>
</tr>
<tr>
<td>Pulmonary status (n = 19, 13 boys)</td>
<td></td>
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<tr>
<td>Holzer score</td>
<td>0.9 ± 0.2 (0–2)</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>83 ± 5 (44–127)</td>
</tr>
<tr>
<td>Gastrointestinal status</td>
<td></td>
</tr>
<tr>
<td>Pancreatic insufficient (n = 19, 13 boys)</td>
<td></td>
</tr>
<tr>
<td>Fat absorption (%)</td>
<td>86.4 ± 1.6 (74–94)</td>
</tr>
<tr>
<td>Diet (n = 18, 12 boys)</td>
<td></td>
</tr>
<tr>
<td>Energy (% of RDI)</td>
<td>89 ± 4 (57–133)</td>
</tr>
<tr>
<td>Protein (% of RDI)</td>
<td>230 ± 14 (127–339)</td>
</tr>
<tr>
<td>Sodium (mg·kg−1·d−1)</td>
<td>89 ± 7 (50–145)</td>
</tr>
<tr>
<td>Potassium (mg·kg−1·d−1)</td>
<td>89 ± 6 (42–128)</td>
</tr>
<tr>
<td>Plasma electrolytes (n = 19, 13 boys)</td>
<td></td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>103.9 ± 0.3 (102–108)</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>140.2 ± 0.6 (137–144)</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.6 ± 0.1 (3.4–5.2)</td>
</tr>
</tbody>
</table>

Comparison of TBCl and TBK with TBW(D2O)

There was a relatively strong linear correlation between the sum of TBCl and TBK and TBW(D2O), as shown in Figure 1. The sum of TBCl and TBK was a significant predictor of TBW(D2O) (P < 0.001), accounting for 79% of the variation in TBW(D2O).

Comparison of TBW(Cl + K) with TBW(D2O)

Absolute mean values of TBW(D2O) and TBW(Cl + K) in boys and girls and in the combined group are shown in Table 3. The paired t test showed no significant difference between the 2 estimates of TBW. In addition, no significant sex difference was found in estimates of TBW by either method when the unpaired t test was used.

A linear regression analysis of TBW(D2O) compared with TBW(Cl + K) in the CF group showed TBW(Cl + K) to be a significant predictor of TBW(D2O) (P < 0.001). The slope of the regression line was not significantly different from 1.0 (one-sample t test), and the intercept was not significantly different from 0 (one-sample t test).

Results from the Bland and Altman analysis of agreement between the D2O dilution method and the method of summing TBCl and TBK are summarized in Table 4 and Figure 2. The 95% CI for the average measurement bias between the 2 methods included zero both for boys and girls and for the combined group. For individual subjects, the variation of differences between the 2 methods are indicated by the limits of agreement, which spanned 4.95 L in boys, 2.87 L in girls, and 4.69 L in the combined group. Also, measurement biases between the 2 methods were not significantly associated with age, sex, genotype.

Laboratory assessment

Seven subjects (5 boys) were homozygous for the ΔF508 allele, 9 (6 boys) were heterozygous for the ΔF508 allele, and 3 (2 boys) had no ΔF508 allele. The CF group had plasma chloride, sodium, and potassium concentrations within the control reference ranges. Plasma chloride and potassium concentrations showed no significant association with age, sex, genotype expressed in terms of the ΔF508 allele, steroid use, or any of the variables of anthropometry, growth, pulmonary status, gastrointestinal status, or diet.

Body-composition assessment

General effects of cystic fibrosis on body composition

The body composition of the 19 subjects studied is summarized in Table 2. Deficits were observed for both age- and height-standardized values of TBCl, TBK, and TBW. Negative linear correlations were observed between age and age-standardized values of TBCl (r² = 29.2, P = 0.02), TBK (r² = 30.6, P = 0.01), and TBW (r² = 41.2, P < 0.01) considered separately. By contrast, mean values for the ratios (TBCl + TBK)/TBW and TBCl/TBK did not differ significantly from the cited reference values. Neither of these ratios was significantly associated with age, genotype expressed in terms of the ΔF508 allele, steroid use, or any of the variables of anthropometry, growth, pulmonary status, gastrointestinal status, or diet. Sex did not significantly affect any body-composition measure.

![Figure 1](https://example.com/figure1.png)

![Figure 2](https://example.com/figure2.png)

TABLE 2
Body-composition assessment of children with cystic fibrosis1

<table>
<thead>
<tr>
<th>Variable (mmol/mmol)</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBCl (n = 19, 13 boys)</td>
<td>1097 ± 34 (824–1362)</td>
</tr>
<tr>
<td>Percentage TBCl for age (%)</td>
<td>88.2 ± 2.9 (63.5–113.4)</td>
</tr>
<tr>
<td>Percentage TBCl for height (%)</td>
<td>92.4 ± 2.5 (68.1–118.2)</td>
</tr>
<tr>
<td>TBK (mmol) (n = 19, 13 boys)</td>
<td>1717 ± 51 (1269–2059)</td>
</tr>
<tr>
<td>Percentage TBK for age (%)</td>
<td>91.7 ± 2.1 (81.1–114.3)</td>
</tr>
<tr>
<td>Percentage TBK for height (%)</td>
<td>94.9 ± 1.5 (84.6–105.6)</td>
</tr>
<tr>
<td>TBW1 (L) (n = 19, 13 boys)</td>
<td>19.4 ± 0.5 (15.6–23.8)</td>
</tr>
<tr>
<td>Percentage TBW for age (%)</td>
<td>94.9 ± 2.4 (81.1–121.5)</td>
</tr>
<tr>
<td>Percentage TBW for height (%)</td>
<td>95.5 ± 1.4 (86.2–107.2)</td>
</tr>
<tr>
<td>TBCl + TBK/TBW2 (mmol/mmol)</td>
<td>145.3 ± 1.9 (126.2–155.7)</td>
</tr>
<tr>
<td>TBCl/TBK (mmol/mmol)</td>
<td>0.64 ± 0.01 (0.49–0.79)</td>
</tr>
</tbody>
</table>

1 ± SEM; range in parentheses; CF, cystic fibrosis; TBCl, total body chloride; TBK, total body potassium; TBW, total body water.

2 Significantly different from 100% (one-sample t test): *P < 0.05, **P < 0.01, ***P < 0.001.

3 Measured by D2O dilution.

4 Not significantly different from reference values: 4146 mmol/L, 70.66 mmol/mmol.
expressed in terms of the ΔF508 allele, steroid use, or any of the variables of anthropometry, growth, pulmonary status, gastrointestinal status, or diet.

**DISCUSSION**

**Effect of mild symptoms of cystic fibrosis on TBCl, TBK, and TBW**

The CF group in this study had a body-composition pattern consistent with compromised growth of new tissue and loss of existing tissue. This was evidenced by 1) significant deficits in age- and height-standardized measures of TBCl, TBK, TBW, and body weight; 2) age-standardized deficits in TBCl, TBK, TBW, and body weight that increased significantly with age; and 3) a subnormal weight velocity. By contrast, individual subjects appeared capable of attaining normal TBCl, TBK, TBW, or body weight for age or height.

There is a paucity of TBCl data from subjects with CF. Measurements of TBCl in apparently well-nourished children with CF were recorded (IRJ Humphries and KJ Gaskin, unpublished observations, 1996). TBCl was determined by IVNAA in 55 fibrocystic children with an average age of 10.8 y and 28 healthy children with an average age of 11.1 y. Overall, the CF group weighed 8 kg less and had 8% less TBCl than did the control group. However, when TBCl was adjusted for body weight, there was no significant difference in TBCl between the 2 groups. Humphries and Gaskin concluded that, on a body-weight basis, well-nourished children with CF have normal amounts of TBCl. The only other report of TBCl in subjects with CF appears to be that of Cheek (4), who used the NaBr dilution technique to measure TBCl in 5 malnourished, fibrocystic children aged between 0.5 and 4 y. Four of the 5 children had an increased ratio of TBCl to body weight; this finding was interpreted to signify a loss of total body fat. The TBCl observations in the present study extend the findings of Cheek (4) and are consistent with the data of Humphries and Gaskin. The TBK and TBW observations in this study support results of past studies showing that children with CF can attain normal amounts of TBK and TBW and that age- and height-related deficits in TBK and TBW develop in relation to the severity of CF symptoms (10–12, 36–38).

Multiple factors may affect TBCl, TBK, and TBW in children with CF. These include the normal influences of age, sex, growth, and physical activity (8, 26, 29–32, 39, 40) and the abnormal influences of malnutrition secondary to pulmonary and gastrointestinal symptoms of CF (12, 41, 42) and inadequate dietary intake (1, 43, 44). In this study, CF-related lung disease, pancreatic insufficiency, and an inadequate dietary energy intake were the factors most likely to influence body-composition abnormalities. This statement is supported by the observation that 18 of 19 subjects had minimal or mild symptoms of lung disease. Also, all subjects were pancreatic insufficient, and the CF group reported a reduced dietary energy intake equivalent to 89% of the RDI (see Table 1).

**Comparisons between TBCl, TBK, and TBW**

The results of this study suggest that children with mild symptoms of CF can maintain normal relations among TBCl, TBK, and TBW. This is supported by the following findings. First, a positive linear correlation was observed between TBCl + TBK and TBW (see Figure 1). This result was independent of sex. Second, there was no significant difference in TBW by either method, 
P > 0.05 (unpaired t test).

**TABLE 3**

<table>
<thead>
<tr>
<th></th>
<th>TBW(D$_2$O)</th>
<th>TBW(Cl + K)</th>
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<tbody>
<tr>
<td>Boys (n = 13)</td>
<td>19.2 ± 0.7 (15.6–23.8)</td>
<td>18.5 ± 0.7 (14.4–22.8)</td>
</tr>
<tr>
<td>Girls (n = 6)</td>
<td>19.8 ± 0.6 (16.9–20.9)</td>
<td>20.1 ± 0.7 (17.4–21.7)</td>
</tr>
<tr>
<td>Combined$^a$ (n = 19)</td>
<td>19.4 ± 0.5 (15.6–23.8)</td>
<td>19.0 ± 0.5 (14.4–22.8)</td>
</tr>
</tbody>
</table>

$^a$ SEM; range in parentheses.

$^b$ Nonsignificant sex difference in TBW by either method, 
P > 0.05 (unpaired t test).

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**FIGURE 1.** Total body water as measured by D$_2$O dilution [TBW(D$_2$O)] compared with the sum of total body chlorine plus total body potassium (TBCl + TBK) in 19 children (13 boys) with cystic fibrosis. Regression equation: TBW(D$_2$O) = 0.00594 x + 2.67 (SEE = 1.09 L, $r^2 = 0.79$, P < 0.001).
dent of sex. Because TBCl is largely confined to the extracellular compartment (≈88% by weight) (3, 7), TBCl should be related to the volume of this compartment. Similarly, TBK is largely confined to the intracellular compartment (> 96% by weight) (7, 33) and should therefore be related to the volume of this compartment. The observed correlation is not unexpected and is consistent with similar findings reported in healthy children of similar age (26) and in healthy adults (5).

Second, the ratio (TBCl + TBK)/TBW(D2O) in the CF group attained a mean (–SEM) value of 145.3 ± 1.9 mmol/L, which was similar to the control value of 146 mmol/L calculated from the reference data of Cheek (26). Although this ratio showed wide variability in individual subjects (126.2–155.7 mmol/L), the ratio was not significantly associated with age, sex, or the measures of anthropometry, growth, genotype, pulmonary and gastrointestinal status, diet, or steroid use.

Third, the ratio TBCl/TBK was not significantly different from the control value derived from the reference data of Cheek (see Table 2). Our results are consistent with those of past studies of healthy humans that showed the ratio TBCl/TBK falling within a relatively constant range from ≈0.6 to ≈0.8 mmol/mmol during childhood, adolescence, and adulthood (26, 28).

The relation of TBCl to ECW

In healthy children and adults, ≈88% of TBCl is located in disparate pools of extracellular fluid (3, 7). Although chlorine concentrations of extracellular fluids may vary considerably, the average chlorine concentration of the total ECW pool is closely approximated by the chlorine concentration of blood plasma (≈100 mmol/L).

The intrinsic defect identifying CF is abnormal transepithelial chloride transportation. Whether this defect is associated with TBCl abnormalities in CF patients was questioned previously. The results of the present study suggest that children with mild symptoms of CF can maintain a normal relation between TBCl and ECW. Subjects showed a normal plasma chlorine concentration consistent with that reported in previous studies (45–47). This study also found a strong linear correlation and a good agreement between TBW(Cl + K) and TBW(D2O). In calculating ECW from TBCl, we assumed that 88% of TBCl is found in ECW and that the plasma chlorine concentration is representative of the average chlorine concentration of the total ECW pool. Our results suggest that these assumptions are suitable for clinically stable children with mild symptoms of CF.

The relation of TBK to ICW

This study identified the following supportive evidence for a normal relation between TBK and ICW in clinically stable children with mild symptoms of CF. First, plasma potassium concentrations were within the normal reference range for 17 of 19 subjects, slightly above the upper reference value for one subject (5.2 compared with 5.0 mmol/L), and slightly below the lower

![FIGURE 2. Differences between total body water measured by D2O dilution [TBW(D2O)] and TBW estimated from the sum of total body chlorine plus total body potassium [TBW(Cl + K)] in 19 children (13 boys) with cystic fibrosis. The mean difference (bias), the 95% CI of the mean difference, and the limits of agreement are also shown.](https://academic.oup.com/ajcn/article-abstract/71/1/36/4729132/fig2)
reference value for another (3.4 compared with 3.5 mmol/L).

Second, we observed a strong linear correlation and a good agreement between TBW(Cl + K) and TBW(D$_2$O). ICW was derived from TBK by using a cellular model that assumes that 100% of TBK is found in the body cell mass, that the ratio of body cell mass to TBK is 0.00833 kg/mmol, and that 75% of the body cell mass is ICW by weight (33, 34). Our data suggest that this cellular model of TBK is also suitable in children with mild symptoms of CF.

The validity of TBW measurements by D$_2$O dilution

This study used the D$_2$O dilution method as a reference standard against which TBW estimates derived from TBCl + TBK were compared. In an ancillary experiment performed in the CF group, no significant difference was observed between TBW measured by D$_2$O dilution and TBW derived from the 4-compartment model of body composition defined as body weight (measured by using digital scales) minus the sum of total body fat measured by dual-energy X-ray absorptiometry, total body protein determined by IVNAA, and total body bone mineral measured by dual-energy X-ray absorptiometry (33 ± SEM: 19.4 ± 0.5 compared with 19.6 ± 0.5 L for TBW(D$_2$O) and TBW(4-compartment model), respectively; $P = 0.36$ by paired t test) (21, 22). The significance of this comparison is that the 4-compartment model is based on methods that are independent of the primary CF defect.

Summary

This study showed independent, cross-sectional measurements of TBCl, TBK, and TBW in a group of clinically stable prepubertal children with mild symptoms of CF. Modest deficits in TBCl, TBK, and TBW were consistent with the effect of chronic energy malnutrition secondary to multiple factors that included CF lung disease, pancreatic insufficiency, and an energy-deficient diet. By contrast, relations among TBCl, TBK, and TBW appeared normal and unaffected by symptoms of CF. The clinical significance and implications of these findings are as follows. First, the abnormal CF gene that affects electrolyte and fluid transport across the epithelial surfaces of specific tissues and organs does not appear to affect to any significant extent normal relations between electrolytes and water compartments at a whole-body level. Second, noninvasive measurements of TBCl and TBK may be used as surrogate measures of ECW, ICW, and TBW in clinically stable children with mild symptoms of CF.

We extend our appreciation to the children and parents who willingly participated in this study. We also gratefully acknowledge the support of Colin Robertson from the Department of Thoracic Medicine, Royal Children’s Hospital, and Mark Wahqvist from the Department of Medicine, Monash Medical Centre, and the technical assistance of Ding Wei Xiong from the Department of Medicine, Monash University, and Susan Forrest from the Murdoch Institute, Melbourne.

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