Adequacy of clinical formulae for estimation of energy requirements in children with cystic fibrosis

John J Reilly, T John Evans, Jane Wilkinson, James Y Paton

Abstract

Background—Two clinical formulae (CF conference formula and estimation based on 120% of average requirement for energy) have been recommended for the estimation of energy requirements in cystic fibrosis but their accuracy is unknown.

Aim—To compare the accuracy of estimates of energy requirement derived from the two formulae.

Methods—Energy requirement, defined as total daily energy expenditure, was measured using the doubly labelled water method in 15 patients (six girls, nine boys; mean (SD) age, 10.0 (2.4) years) who were well and clinically stable. The accuracy of the formulae was assessed using calculation of biases and limits of agreement relative to measured energy requirement.

Results—Estimates from the CF conference formula were lower than measured values (mean paired difference, 0.52 MJ/day; 95% confidence interval (CI), −1.10 to 0.10), but this bias was not significant, and was smaller than that from the alternative formula (mean paired difference, 0.77 MJ/day; 95% CI, −0.20 to 1.74). Limits of agreement relative to measured total daily energy expenditure were narrower for the CF conference formula (−2.72 to 1.68 MJ/day) than for that based on 120% of estimated average requirement (−2.75 to 4.29 MJ/day), but with both formulae errors in estimation at the individual level were large.

Conclusions—The CF conference formula offers improved prediction of energy requirements, but the accuracy of both formulae at the individual level is not sufficiently good for clinical purposes.

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Keywords: cystic fibrosis; energy expenditure; doubly labelled water method

Growth retardation and undernutrition remain common complications of cystic fibrosis (CF).1-4 Effective prevention and/or management of undernutrition in chronic disease requires provision of energy in appropriate amounts to meet energy needs. Although standard formulae are available for estimation of energy needs in childhood,5 these are inappropriate in CF because the disease is characterised by: abnormal body composition5; increased faecal energy losses6; increased resting energy expenditure7-9; reduced physical activity10-12; and a possible increase in total energy expenditure,7 although this has been debated.13-15

In these circumstances, clinical management requires an alternative formula for the estimation of energy requirements. In other chronic diseases of childhood, disease specific formulae have been established,14 15 and their use has potential clinical advantages.16 A CF specific formula for clinical estimation of energy requirements has now been available for some years (the CF conference formula),17 but it has not been tested formally and is not widely used. In the UK, energy requirements of children with CF are usually estimated using an alternative approach, as 120% of the estimated average requirement (EAR) for energy.18-19 The aim of our study was to compare the accuracy of these two formulae for the estimation of energy requirements in children with CF, by comparison with measurements of total energy expenditure using the doubly labelled water method.

Patients and methods

PATIENTS AND STUDY POWER

We recruited 15 children. We excluded patients from the study if they were diabetic, if they were non-compliant, or if they were unwell at the time of the study. Therefore, all patients were well, clinically stable, and living as outpatients at the time of our study. The research was approved by the hospital ethics committee and was carried out with the informed consent of children and their families. The study design used paired comparisons of measured and predicted energy requirement, and the sample size was large enough to detect a bias between estimated and measured energy requirement, which was deemed clinically significant (1.0 MJ/day), with standardised difference 1.0 and power 0.90 at the 5% level.

CLINICAL DATA

We performed standard pulmonary function tests on each child. Genotype and Schwachman score (an index of disease severity) were known for all patients. For descriptive purposes only, growth and nutritional status were assessed by measurement of height to 0.1 cm using a stadiometer (Holtain Ltd, Crosswell, UK), weight to 0.1 kg using an electronic scale (Salter, London, UK), and calculation of body mass index (BMI). From this we calculated...
Estimation of energy requirements in CF

MEASUREMENT OF ENERGY REQUIREMENTS

Total daily energy expenditure (TDEE) was measured over 14 days using the doubly labelled water method and equation A6 of Schoeller, with urine samples obtained from each child predose and then on days 1 and 14. Each child received a weighed, sterilised dose of 1.6 ml/kg 18O (10% enriched) mixed with 0.06 ml/kg 2H (99.9% enriched). Food quotients and energy equivalent of CO2 production were determined from three day household measures records: mean (SD) energy equivalent for CO2 production was 23.7 (0.3) kJ/litre. Isotopic enrichments of samples and diluted doses were analysed in duplicate by isotope ratio mass spectrometry (Bureau of Stable Isotope Analysis, Brentford, Middlesex, UK). Mean (SD) ratio of dilution spaces ([H]/[18O]) was 1.05 (0.02). The energy requirement of a child consists of TDEE plus a small increment to allow for growth (usually <3% of TDEE after the 1st year of life).3

Resting energy expenditure (REE) was measured by ventilated hood indirect calorimetry using the Deltatrac system (Datex Corporation, Helsinoki, Finland), after an overnight fast in nine patients. In six patients, a four hour fast was used because of failure to agree on an overnight fast with the child. Once a “steady state” had been reached, each measurement lasted 12–16 minutes. The mean of two to three measurements was used to calculate resting energy expenditure. Those children on beta-agonist treatment refrained from using it for the period of the fast. The coefficient of variability for this procedure is <3% in our laboratory.28

We measured faecal fat output by quantitative 72 hour collection during the 14 day study period using the Van de Kamer method.27 In each child, dietary fat intake was estimated over three days (one weekend, two weekdays) using a household measures record. The purpose of this was to establish the coefficient of fat absorption (CFA), necessary for the estimation of energy requirements in step 3 of the CF conference formula.

ESTIMATION OF ENERGY REQUIREMENTS

Energy requirements were estimated for each child by following the steps outlined in the CF conference formula. In brief, they were:

Step 1. Estimation of basal metabolic rate (BMR) using the appropriate World Health Organisation (WHO) prediction equation.26

Step 2. Calculation of daily energy expenditure by multiplying BMR by “activity plus disease coefficients”. (1) All children were considered as active (BMR × 1.7 from the formula). (2) Incorporation of disease coefficient based on forced expiratory volume in one second (FEV1) as follows: moderate lung disease (FEV1, 40–79% of predicted), predicted daily energy expenditure = (BMR × (1.7 + 0.2)); severe lung disease (FEV1, <40% of predicted), predicted daily energy expenditure = (BMR × (1.7 + 0.3)).

No correction was made for faecal energy losses in 13 of the patients because these were not deemed large enough to merit an adjustment according to the CF conference criteria (CFA > 0.93). In two patients (numbers 2 and 7), the CFA was lower than the threshold of 0.93. This necessitated calculation of a third step in the formula for these two children.

Step 3. Estimated TDEE = estimated TDEE (from step 2) × (0.93/CFA).

Estimates of energy requirement from the formula were made by one investigator, blind to the calculation of measured energy requirement by another investigator.

STATISTICAL ANALYSIS

Paired differences between measured and estimated energy requirements were calculated and the significance of these determined by paired t test and 95% confidence intervals (CI). Agreement between predicted and measured energy requirements at the level of the individual child was tested using an assessment of bias and “limits of agreement”.19

Results

Table 1 gives clinical and anthropometric characteristics of the patients. As a group, the children were characterised by relatively mild disease with relatively good growth and nutritional status, but the sample included a wide range of disease severity (table 1).

There was a tendency for mean measured total daily energy expenditure to exceed

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Table 1  Characteristics of patients

<table>
<thead>
<tr>
<th>Patient/Sex</th>
<th>Age (years)</th>
<th>Genotype</th>
<th>Kushnerman score</th>
<th>FEV1 (% predicted)</th>
<th>BMI SDS</th>
<th>Height SDS</th>
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<tr>
<td>1/F</td>
<td>9.1</td>
<td>2</td>
<td>90</td>
<td>83</td>
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<td>-1.40</td>
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<td>2/F</td>
<td>12.3</td>
<td>1</td>
<td>85</td>
<td>67</td>
<td>0.18</td>
<td>0.70</td>
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<tr>
<td>3/F</td>
<td>11.0</td>
<td>1</td>
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<td>93</td>
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</tr>
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<td>4/F</td>
<td>5.1</td>
<td>2</td>
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<td>80</td>
<td>-0.98</td>
<td>-0.56</td>
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<tr>
<td>5/F</td>
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<td>6/F</td>
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<td>10/M</td>
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<td>89</td>
<td>0.09</td>
<td>0.40</td>
</tr>
<tr>
<td>11/M</td>
<td>10.8</td>
<td>1</td>
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<td>44</td>
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</tr>
<tr>
<td>12/M</td>
<td>8.9</td>
<td>1</td>
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<td>98</td>
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<tr>
<td>13/M</td>
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<td>2</td>
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<td>51</td>
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<tr>
<td>14/M</td>
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<tr>
<td>15/M</td>
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<tr>
<td>Mean</td>
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<td>79</td>
<td>-0.23</td>
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<tr>
<td>SD</td>
<td>2.4</td>
<td>13</td>
<td>22</td>
<td>0.81</td>
<td>0.90</td>
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</table>

Genotype: 1, homozygous for ΔF508; 2, heterozygous for ΔF508; 3, other. SDS, standard deviation score; FEV1, forced expiratory volume in one second.
Table 2 Measured and predicted energy expenditure

<table>
<thead>
<tr>
<th>Patient</th>
<th>TDEE (MJ/day) measured</th>
<th>TDEE (MJ/day) predicted*</th>
<th>TDEE (MJ/day) predicted (1.2 × EAR)</th>
<th>REE (MJ/day)* measured</th>
<th>REE* (MJ/day) predicted</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>7.82</td>
<td>7.58</td>
<td>8.74</td>
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<td>8</td>
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<td>9.89</td>
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<td>4.08</td>
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<td>9.89</td>
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<td>11.90</td>
<td>13.81</td>
<td>8.06</td>
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<td>8.76</td>
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<td>11.12</td>
<td>6.58</td>
<td>4.91</td>
</tr>
<tr>
<td>14</td>
<td>8.92</td>
<td>7.58</td>
<td>9.89</td>
<td>5.28</td>
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<td>15</td>
<td>10.32</td>
<td>9.50</td>
<td>11.12</td>
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<td>5.00</td>
</tr>
<tr>
<td>Mean</td>
<td>9.35</td>
<td>8.83</td>
<td>10.10</td>
<td>5.68</td>
<td>4.83</td>
</tr>
<tr>
<td>SD</td>
<td>1.93</td>
<td>1.66</td>
<td>1.42</td>
<td>1.98</td>
<td>0.72</td>
</tr>
</tbody>
</table>

* Differences between predicted (WHO formula) and measured REE significant (paired t test, p < 0.05). Other differences between measured and predicted values were not significant.

EAR, estimated average requirement; REE, resting energy expenditure; TDEE, total daily energy expenditure.

Discussion

Our study showed that both of the clinical formulae for estimating energy requirements of patients with CF were associated with large errors at the level of the individual patient (fig 1). The evidence that the bias in estimating TDEE was larger, and limits of agreement wider, when using the simple formula 120% of EAR (fig 1) was not unexpected given the relatively crude nature of this approach and its failure to individualise for activity level, severity of lung disease, and degree of malabsorption. However, this formula is very popular in clinical practice and our results are useful in providing both a quantitative estimate of the errors that arise when it is used, and of its disadvantages relative to the CF conference formula.

Although errors arising from both formulae at the group level were not significant, the limits of agreement that we calculated represent prediction intervals for individual estimates of energy requirement. The prediction interval for the formula 120% of EAR ranged from −2.8 to 4.3 MJ/day; that is, from an underestimate of 2.8 MJ/day to an overestimate of 4.3 MJ/day at the individual level. The prediction interval for the CF conference formula was narrower (−2.7 to 1.7 MJ/day), although this means that errors in estimation at the individual level were also rather wide. Therefore, we recommend that both formulae are used with caution when estimating energy requirements of individual children. Both formulae are best considered as a “starting point” in estimation, and any judgment of energy needs should be titrated against clinical observations of adequate growth and nutritional status. It is also worth noting that these formulae estimate a minimum energy requirement, and an increment to allow for growth and nutritional repletion should be added when determining the diet prescription.

Accurate estimation of energy requirements of individuals is difficult, even in healthy children, and might not be achievable using a simple clinical algorithm. Development of better simple algorithms for estimating energy requirements of groups of children is probably more realistic. This might be achievable without further research, because a number of
Estimation of energy requirements in CF

studies have now measured TDEE by the dou-

bly labelled water method in children with CF: pooling these data could provide improve-

ments to the existing CF conference formula.

In this case, a number of options could be

considered. Predicted BMR from the WHO

formula underestimated REE in our patients

with CF, as expected.18 Use of measured

REE, where practical, would remove this bias,

but might not dramatically improve prediction

for individual children. When we incorporated

measured REE in place of predicted BMR into

the CF conference formula, bias became posi-

tive (0.81 MJ/day), but limits of agreement

were still rather wide at −1.35 to 2.90 MJ/day.

The absence of a dramatic improvement in

accuracy of prediction with the use of measured

REE also suggests that much of the error for

an individual patient lies in the correction for

physical activity. Bias in estimates from the

CF conference formula was not related to the

size of the TDEE, and so could easily be cor-

rected statistically. However, this would not
deal with the problem of errors at the indi-

vidual level. Physical activity level and/or

TDEE can only be established for indi-

viduals using techniques such as doubly

labelled water,19 which are not suitable for

most clinical settings, so the limitations of any

approach based on clinical estimation might

have to be accepted. In addition, body com-

position is relevant to energy requirements,10

but its measurement would again present serious

problems in most clinical settings. Lung function

might also be relevant. In our study, and in others,5
% predicted FEV1, significantly correlated with

nutritional status (BMI SDS: r = 0.52, p < 0.05) and severity of

lung disease might be an important determi-

nant of energy requirement in CF.11 However, the

complexity of an algorithm that included

measurement of body composition, lung func-

tion, and physical activity level would probably

preclude clinical use.

Alternative approaches to determination of

energy requirements of individual children are

available, but have limitations and are not

always practical in the clinical setting. One

technique that can provide accurate group esti-

mates is to use the measurement of energy

intake from gastrostomy fed patients.12 If such

patients are growing well, their energy intake

will represent their energy requirement and so

can be used to estimate energy requirement.

However, this approach is time consuming,

restricted to those children fed by gastrostomy,

and does not allow estimation of requirement

before the diet prescription is determined. For

the child who has CF with reasonable growth

and nutritional status, energy requirements are

probably being met adequately. For children

with poor growth or nutritional status, where a

decision is taken to initiate supplementary

feeding, or when a group estimate is required

for research purposes (to design a nutritional

supplementation study for example), a clinical

formula might be a useful starting point.

The CF consensus conference7 noted that, for

the child and adolescent with CF, individu-

alisation of the diet prescription, using appro-

priate methods of estimation, is an important
element of nutritional management. This

remains true given the relatively high preval-

ee of undernutrition seen in this patient popula-

tion,13 and the emphasis on diet prescription/nutritional sup-

port as a central element of clinical manage-

ment. We conclude that the available formulae for

children with CF do not permit sufficiently accurate estimates of energy

requirement for clinical use with individual patients. Measurement of total energy expendi-

ture would be more accurate, but impractical

for most clinical settings.

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and their families for their enthusiasm and willingness to

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the manuscript.

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Ketogenic diet again

When I was a young doctor I was once given the task of approaching a national chain store for a supply of free cream so that a family could afford to start their child on a ketogenic diet. I have followed the ups and downs of the diet’s popularity since then with some interest (but I’ve never had to beg again). It was first used for difficult childhood epilepsy in the USA in the early 1920s. At Johns Hopkins Hospital it has been in use since the 1930s and paediatric neurology staff there retain their enthusiasm for it. They have reported its use in 150 consecutive children (John M Freeman and colleagues. Pediatrics 1998;102;1358–63). Over a period of 24 months in 1994–96 the diet was prescribed for 150 children aged 1–16 who had a mean of 410 seizures a month despite having been treated with an average of more than six antiepileptic drugs. By three months seizure frequency had decreased by 50% or more in 89 (55%) children and by 90% or more in 50 (33%). By one year these figures were 50% and 27%. Younger children were somewhat more likely to respond but seizure type or sex made no significant difference although, as might be expected, many of the children had refractory seizure types of the kind often seen in Lennox-Gastaut syndrome. Fifty five per cent remained on the diet at one year and those who stopped it usually did so because it was not effective.

The Johns Hopkins team consider the ketogenic diet to be more effective for these children than many of the newer drugs, and their families are usually prepared to carry on with it as long as they feel it is effective. Some of the success could possibly be related to the fact that the same dietician has been in charge of the diet at Johns Hopkins for many years.
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