Energy requirements for growth and development in infancy\textsuperscript{1–3}

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ABSTRACT Current international recommendations for energy requirements are based on >9000 measurements of energy intake in both breast- and formula-fed infants. The measurement of energy intake in babies is far from straightforward and the possibility of significant error is great. The opportunity now exists, however, to compare current recommendations with measurements of total energy expenditure (TEE) obtained via the doubly labeled water technique. Approximately 300 measurements of TEE in the first year of life have been made in normal, healthy babies. These data show that estimates of energy intake derived from the measurements of TEE are considerably below the current international recommendations. The same technique has also allowed the energy requirements of sick infants to be evaluated. Two examples are highlighted of infants born small for gestational age and infants born with cystic fibrosis. First, data collected from babies born small for gestational age suggest that such infants have a TEE and hence requirement ≈20% above that found in infants born with a weight appropriate for their gestational age. This information will be relevant to those professionals attempting to supply optimum nutrition to babies born small for gestational age. Second, in cystic fibrosis it has been suggested that, concurrent with the basic features of the disease, there is an energy-wasting lesion that will increase TEE and hence energy requirement. Recent data collected from babies with cystic fibrosis strongly suggest that this is not the case, and previous data were confounded by subclinical disease status. Am J Clin Nutr 1998;68(suppl):939S–43S.

KEY WORDS Energy expenditure, energy intake, infants, doubly labeled water, cystic fibrosis

INTRODUCTION

Studies in the field of energy metabolism, no matter how complex, revolve around the fundamental energy balance equation that equates energy intake to energy expenditure and energy stored. It follows, therefore, that a basic requirement of many studies in this field will be the ability to measure one or all of the terms within the energy balance equation. It would not be an overstatement to say that the development of the doubly labeled water technique for use in humans has enabled such measurements to be obtained with an accuracy, precision, and validity that was previously impossible.

After the validation studies in adults in the early 1980s (1, 2), similar studies soon followed in pediatric subjects (3–6) that established both the viability of the doubly labeled water technique in such subjects and the accuracy, which ranged from 0.3% to 5.0%, when compared with measurements obtained from indirect calorimetry.

During infancy there is the potential for several marked deviations from the theoretical model (7) that could potentially impinge on the accuracy of the technique. The effect of these deviations, including changing nutrition, rapid growth, and rapid water turnover, were assessed (8, 9) and the data suggest that the model is reasonably robust and with some slight changes, e.g., dose regimens and sampling procedures, good data can be obtained.

Over the past 12 y, the doubly labeled water technique has been used in many studies that aimed to explore energy metabolism during infancy. Infants are popular subjects for several reasons. First, there were many questions pertaining to energy metabolism that required answers in this population that included more accurate definitions of energy requirements in health and disease. Second, studies in infants were financially viable compared with older children and adults because of the high cost of the stable isotope $^{18}$O, which is given in a dose relative to body weight.

This review will highlight 2 areas in which the doubly labeled water technique has been applied to infants. First, it has been used to evaluate energy requirements in healthy infants during the first year of life, and second, several clinical conditions have been studied to evaluate whether energy requirements differ in such situations. Two specific examples will be considered in the second part of this review, namely infants born small for gestational age and infants born with cystic fibrosis.

ENERGY REQUIREMENTS IN HEALTHY INFANTS

Since the validation studies carried out in the 1980s, there have been ≈450 measurements of total energy expenditure in infants worldwide. Most of these studies can be divided into 2 types. First, several studies investigated the relation between energy expenditure and energy balance in infancy and later growth, development, and behavior. Second, studies investigated energy expenditure and, hence, energy requirements in health and disease.

The first group of studies is beyond the scope of the present

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review. This section of the review will focus on the studies that compared measurements of total energy expenditure with contemporary recommendations for energy intake in healthy infants (10).

International recommendations to date have been based on data that relate to measured energy intake in the first year of life. The concept of determining and publishing national and international recommendations for energy requirements in infancy dates back almost 50 y. The first international publication in 1950 recommended a constant value of 420 MJ·kg⁻¹·d⁻¹ (100 kcal·kg⁻¹·d⁻¹) for the first year of life (11). The subsequent 1957 publication (12) acknowledged that energy requirements were higher in the first few months of life and so recommended an intake of 500 MJ·kg⁻¹·d⁻¹ (120 kcal·kg⁻¹·d⁻¹) for the first 3 mo, with this value falling in a stepwise manner to 420 MJ·kg⁻¹·d⁻¹ (100 kcal·kg⁻¹·d⁻¹) at 12 mo of age. The 1973 recommendations (13) were very similar to those they superseded; however, further steps were introduced in the fall from 500 MJ·kg⁻¹·d⁻¹ in the first 3 mo of life to 440 MJ·kg⁻¹·d⁻¹ (105 kcal·kg⁻¹·d⁻¹) at age 1 y. The most recent recommendations (14) show more of a departure from the previous 3 publications. The 1985 recommendations are based on an analysis of all the available data for measured energy intake in the first year of life published between 1940 and 1980 (15). The analysis considered over 9000 measurements of energy intake in both breast- and formula-fed infants. There was a curvilinear relation between energy intake and age. The recommendations for energy requirements from the 4 reports are shown in Figure 1. The curvilinear 1985 recommendations can be seen clearly.

The curve produced from the 1985 recommendations was the mathematical best fit to the data. However, it can be explained biologically, as follows. In the first few months of life, growth of both the fat and fat-free components of the body are rapid, with as much as one-third of energy intake being used for growth. However, this figure drops quickly so that by 6 mo of age only about 6% of energy intake is used for growth. After this time, most infants become more mobile and thus the energy cost of physical activity increases, which is reflected in the gradual increase in energy requirement between 6 mo and 1 y of age. However, it has long been accepted that the measurements of energy intake on which these recommendations are based are not straightforward. Test weighing in breast-fed infants is time consuming, invasive in relation to the mother-infant dyad, and makes assumptions about the energy content of breast milk that may not be accurate (16). Calculation of energy intake in formula-fed infants is easier if the child is being fed ready-to-feed formula, but if the formula is being made up by the caregiver, large variations in energy density can be produced (17).

Thus, the opportunity to compare current recommendations for energy requirements with measurements of energy expenditure derived from the doubly labeled water technique was seized by several research groups around the world. It should be remembered that the doubly labeled water technique measures total energy expenditure; to derive an estimate for energy intake, an allowance for energy stored in new tissue must be added to the measure of energy expenditure. As was stated previously, this energy cost is especially high in the first few months of life and cannot be ignored. Fortunately, there are several ways in which the energy stored in new tissue can be calculated. The most straightforward approach is to record the change in body weight of infants over the period of time that energy expenditure is being measured. In infants this is normally 7 d. An assumption can be made that each gram of body weight gained (or lost) has an energy density of 23 kJ (5.6 kcal) (14). Thus, the energy cost of growth can be estimated. For example, if an infant gained 40 g over the 7-d study period, 940 kJ (224 kcal) energy was stored during this time. To obtain a measure of daily energy intake, a value of 135 kJ (ie, 940/7) must be added to the figure for total energy expenditure obtained from the doubly labeled water technique. This approach, therefore, allows the calculation of each infant’s specific energy stored. It should be remembered, however, that in this approach it is assumed that new tissue has a consistent energy density. Certainly, in premature infants or infants recovering from malnutrition, there is evidence that the energy density of new tissue is different from 23 kJ/g (5.6 kcal/g), so care should be taken in using the appropriate values (14).

Another approach to this problem is to use reference data (18) on the rates of deposition of fat and fat-free mass at the age of the infants studied, assign an appropriate energy value to the tissue deposited, calculate the energy stored, and add this value to the measured total energy expenditure. This approach takes into account the fact that weight gain will consist of tissues of varying energy density but assigns the same amount of energy stored to all infants studied at any given age. Again, it is vital that the age of the infant be taken into account in the calculation because rates of fat and protein deposition change dramatically in the first year of life.

By combining the best features of the 2 approaches it is possible to measure the change in body composition over the study period rather than make assumptions. This usually involves the measurement of body composition at the end of the study period as well as at the beginning, with use of stable isotopes, but this approach at least allows an individual value for energy stored to be calculated for each baby on the basis of the measured change in body composition. The assessment of body composition using stable isotopes has a precision of ≈1%, and it is important to remember that the deuterium dilution space is ≈4% grace is ≈1% greater than true total body water and that the ¹⁸O₂ dilution spreader than true total body water (19). These differences are due to exchange of isotope with nonaqueous hydrogen and oxygen in the body.
TABLE 1
Data relating to the major studies of total energy expenditure in healthy infants in the first year of life

<table>
<thead>
<tr>
<th>Reference and study specifics</th>
<th>Total energy expenditure $^2$ (kcal·kg$^{-1}$·d$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasquez-Velasquez (20)</td>
<td>$n = 8$MF, 0–3 mo of age 340 ± 55 (82 ± 23)</td>
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<tr>
<td></td>
<td>$n = 15$MF, age 3–6 mo of age 325 ± 90 (78 ± 21)</td>
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<tr>
<td></td>
<td>$n = 19$MF, age 6–9 mo of age 335 ± 65 (80 ± 16)</td>
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<tr>
<td></td>
<td>$n = 8$MF, age 9–12 mo of age 335 ± 50 (85 ± 12)</td>
</tr>
<tr>
<td>Roberts et al (21)</td>
<td>$n = 18$MF, 3 mo of age 300 ± 20 (72 ± 5)</td>
</tr>
<tr>
<td>Davies et al (22)</td>
<td>$n = 39$MF, 1.5 mo of age 270 ± 70 (64 ± 17)</td>
</tr>
<tr>
<td></td>
<td>$n = 40$MF, 3 mo of age 280 ± 60 (67 ± 14)</td>
</tr>
<tr>
<td></td>
<td>$n = 37$MF, 6 mo of age 330 ± 50 (79 ± 12)</td>
</tr>
<tr>
<td>Butte et al (23)</td>
<td>$n = 10$BF, 1 mo of age 270 ± 50 (74 ± 14)</td>
</tr>
<tr>
<td></td>
<td>$n = 10$BF, 1 mo of age 280 ± 35 (67 ± 8)</td>
</tr>
<tr>
<td></td>
<td>$n = 10$BF, 4 mo of age 270 ± 35 (64 ± 8)</td>
</tr>
<tr>
<td></td>
<td>$n = 10$BF, 4 mo of age 305 ± 40 (73 ± 9)</td>
</tr>
<tr>
<td>Butte et al (24)</td>
<td>$n = 19$BF, 4 mo of age 310 ± 60 (74 ± 14)</td>
</tr>
<tr>
<td></td>
<td>$n = 19$BF, 6 mo of age 320 ± 30 (76 ± 7)</td>
</tr>
<tr>
<td>Wells (25)</td>
<td>$n = 42$MF, 3 mo of age 325 ± 55 (77 ± 13)</td>
</tr>
<tr>
<td>Davies et al (26)</td>
<td>$n = 16$MF, 9 mo of age 310 ± 55 (74 ± 14)</td>
</tr>
<tr>
<td></td>
<td>$n = 18$MF, 12 mo of age 315 ± 55 (75 ± 14)</td>
</tr>
</tbody>
</table>

$^1$MF, mixture of breast-fed and formula fed; BF, breast-fed; FF, formula fed.

$^2$x ± SD.

The major studies to date that have reported measurements of total energy expenditure in healthy infants are shown in Table 1 (20–26). In cases in which data collected by different research groups appear in more than 1 publication, the publication containing the largest data set was used. The table does not include the infants studied by Fjeld et al (27) because these infants were recovering from malnutrition, which may have had a significant effect on the energy metabolism of the infants. It should be remembered that the data shown in Table 1 are for measurements of total energy expenditure, and an increment for the energy cost of growth or energy stored must be added to these data to derive estimates of energy intake and, hence, requirements. This calculation has been made by using the data published recently by Butte (28) to increment the data in Table 1. The subsequent values of calculated energy intake are plotted in Figure 2 against the current 1985 international recommendations (14).

In all cases, the estimates of energy intakes derived from the doubly labeled water technique were considerably below the 1985 recommendations. Also noteworthy is the large range of energy expenditure seen within many of the studies. In some cases the CV is as high as 28%, a surprising finding considering that infants are often thought to behave relatively homogeneously in the first few months of life.

The data shown in Figure 2 for calculated energy intake from studies using doubly labeled water are derived from <400 individuals from around the world. It might be argued that there needs to be a much larger data set available before the current recommendations, which are based on >9000 measurements of energy intake, are challenged. Nevertheless, several factors add weight to the argument that current recommendations are too high. First, measured energy intakes, even when accurate, might not represent desirable intakes. Second, it has long been accepted that measures of energy expenditure are preferable. Third, there should be enough confidence in the accuracy and precision of the doubly labeled water technique (3–6) to suggest that secular changes in energy requirements have occurred. When using the multipoint approach for the assessment of total energy expenditure, precision can be calculated (29) and is normally ~5% (25, 26).

Since the data were collected that forms the basis of the current 1985 international recommendations, infant feeding practices have changed markedly. These changes in feeding practices, including substantial changes in the composition of infant formula, may well account for the differences found between the new data on total energy expenditure and the previous data on energy intake. Moreover, it is also now thought that the energy density of breast milk is lower than previous estimations led us to believe. This may also explain the differences seen in Figure 2.

If national and international recommendations for energy intake in the first year of life are to be reviewed, and possibly changed, in light of the burgeoning data being produced by the doubly labeled water technique, such committees will probably require expanded data as well as evidence that the infants who received the new lower energy intakes grow adequately in childhood. Both of these prerequisites are actively being researched by several groups worldwide.

ENERGY REQUIREMENTS IN CLINICAL CONDITIONS

Whereas data on the energy requirements of normal healthy infants is of great importance, such information should not, and, cannot be assumed to be, correct in many clinical conditions. Many factors may alter energy requirements in disease states, and the need to meet the energy and nutritional requirements of sick infants is important for their recovery. Two examples will now be given of the way in which doubly labeled water has been used to evaluate energy requirements in clinical conditions.

Infants born small for gestational age

Several publications (30–34) suggested that infants born small for gestational age were hypermetabolic and consequently had increased energy requirements. Adequate nutritional management
and growth is dependent on understanding the energy metabolism and pathophysiology of these infants. Disturbances in the body composition of small-for-gestational age infants were also reported (35–36); thus, the interpretation of data relating to energy expenditure in such infants has been difficult. A recent study (37) assessed the relation between total energy expenditure and fat-free mass in a group of small-for-gestational age infants and appropriate-for-gestational-age infants at \( \approx 5 \) wk of age. This study reported that the relation between fat-free mass and total energy expenditure differed significantly between the 2 groups, such that for a given fat-free mass the total energy expenditure in small-for-gestational age infants was \( \approx 20\% \) greater than that found in an appropriate-for-gestational age infant.

Few data suggest that levels of physical activity are increased in 5-wk-old small-for-gestational age infants; thus, it is most likely that the raised total energy expenditure was due to an increase in basal metabolic rate per unit of fat-free mass in these babies. This would be possible if the reduction in cell mass in small-for-gestational age infants was due primarily to a reduction in muscle mass with the more metabolically active organs, such as the liver and brain, being spared. If, therefore, the energy requirements of small-for-gestational age babies, as a population or as individuals, are based on body weight alone, the use of international recommendations will underestimate the nutritional requirement of these vulnerable infants.

**Infants born with cystic fibrosis**

Cystic fibrosis was one of the first clinical conditions in which the doubly labeled water technique was used to assess energy requirements. This condition is one of the most commonly inherited diseases. The defective gene that has been isolated to the long arm of chromosome 7 is inherited in an autosomal recessive manner. The estimated carrier frequency is 1 in 25, resulting in a prevalence of \( \approx 1 \) in 2500 births. The basic feature of the disease is the production of viscous mucus that can cause recurrent pulmonary infection and pancreatic insufficiency.

Evidence suggests that, concurrent with the basic feature above, there was an energy-wasting lesion in the disease that would increase energy expenditure and hence energy requirements. It was suggested that this increase in energy expenditure was not a result of the pathologic effect of the disease per se, such as an increased energy cost of breathing, but was a fundamental energy-wasting lesion. The basis of this hypothesis was the finding that the oxygen consumption in isolated fibroblasts taken from adults with cystic fibrosis was significantly higher than that found in healthy control subjects (38). These early findings prompted the investigation of total energy expenditure in infants with cystic fibrosis by using the doubly labeled water technique (39). In this study, measurements of total energy expenditure were obtained in a group of 9 young children with cystic fibrosis. These children had been diagnosed from neonatal screening and were claimed to be clinically stable and free of acute respiratory infection; there was no evidence of chronic lung disease at the time of the study.

The measurements of total energy expenditure in these children were compared with data from age- and weight-matched control subjects. A significant difference in the total energy expenditure in kJ/kg between the control subjects and the infants with cystic fibrosis was reported. This finding lent more weight to the argument that a fundamental lesion in energy metabolism exists in cystic fibrosis that results in increased energy expenditut and, hence, increased energy requirement, even when the infant was apparently asymptomatic. Nevertheless, it should be remembered that these data on energy expenditure were some of the first to be produced for infants, and the large variation in total energy expenditure found in infants mentioned previously was not fully known. Consequently, as the data on energy expenditure in infants increased, it became apparent that the total energy expenditure in asymptomatic infants with cystic fibrosis was not fundamentally different from that in control subjects (40), and that energy requirements in infants with cystic fibrosis were not increased by an energy wasting lesion. Measurements of total energy expenditure in a group of 18 infants with cystic fibrosis were converted into \( z \) scores to evaluate the normality of energy expenditure of such infants relative to that of healthy infants. This statistical approach was made possible by the expanded literature on energy expenditure in healthy infants that emerged from the development of the doubly labeled water technique. The conclusions of the earlier work (39) were based on a small control group and the measurements of energy expenditure were probably influenced by subclinical disease not detected at the time.

These 2 examples, of energy requirements in small-for-gestational age infants and in infants with cystic fibrosis, illustrate the role that the doubly labeled water technique has had and will continue to have in enabling a greater understanding of energy metabolism, energy expenditure, and energy requirements to be achieved in different groups of infants.

**REFERENCES**


