A cellular-level approach to predicting resting energy expenditure across the adult years¹–³

ZiMian Wang, Stanley Heshka, Steven B Heymsfield, Wei Shen, and Dympna Gallagher

ABSTRACT

Background: We previously derived a whole-body resting energy expenditure (REE) prediction model by using organ and tissue mass measured by magnetic resonance imaging combined with assumed stable, specific resting metabolic rates of individual organs and tissues. Although the model predicted REE well in young persons, it overpredicted REE by ≈11% in elderly adults. This overprediction may occur because of a decline in the fraction of organs and tissues as cell mass with aging.

Objective: The aim of the present study was to develop a cellular-level REE prediction model that would be applicable across the adult age span. Specifically, we tested the hypothesis that REE can be predicted from a combination of organ and tissue mass, the specific resting metabolic rates of individual organs and tissues, and the cellular fraction of fat-free mass.

Design: Fifty-four healthy subjects aged 23–88 y had REE, organ and tissue mass, body cell mass, and fat-free mass measured by indirect calorimetry, magnetic resonance imaging, whole-body ⁴₀K counting, and dual-energy X-ray absorptiometry, respectively.

Results: REE predicted by the cellular-level model was highly correlated with measured REE ($r = 0.92, P < 0.001$). The mean difference between measured REE ($\bar{x} \pm SD$: 1487 ± 294 kcal/d) and predicted REE (1501 ± 300 kcal/d) for the whole group was not significant, and the difference between predicted and measured REE was not associated with age ($r = 0.009$, NS).

Conclusion: The present approach establishes an REE–body composition link with the use of a model at the cellular level. The combination of 2 aging-related factors (ie, decline in both the mass and the cellular fraction of organs and tissues) may account for the lower REE observed in elderly adults.

KEY WORDS Aging, body cell mass, body composition, fat-free mass, magnetic resonance imaging, total body potassium

INTRODUCTION

Aging is associated with a decline in whole-body resting energy expenditure (REE) at a rate of 1–2% per decade after the second decade of life (1). The age-related lowering of REE occurs even when body weight remains stable over the same time period (2). Equations at the whole-body level for predicting REE usually include body weight, height, and age as predictor variables (3).

Fat-free mass (FFM) is an easily measured compartment that is often used to evaluate the body-composition basis of individual differences in REE. FFM also declines with aging, even in the presence of weight stability (4–6). Even after the relation is first controlled for FFM, REE appears to be significantly lower in the elderly (7, 8).

FFM is a heterogeneous compartment with organs and tissues differing widely in metabolic activity. The possibility exists that a lowering of REE with aging can be accounted for by a relatively greater loss of organs with a high metabolic rate. Accordingly, Gallagher et al and other investigators (9–11) measured major organs (liver, brain, heart, and kidneys) and tissues (skeletal muscle and adipose tissue) in a cohort of young adult men and women. The investigators assumed stable organ-tissue-specific resting metabolic rates and measured organ-tissue volumes by magnetic resonance imaging (MRI) to predict whole-body REE. The calculated REE for young subjects was nearly identical to values measured by indirect calorimetry (9). In contrast, the calculated values in older subjects were higher ($\bar{x} \pm SD$) than the measured values by 144 ± 64 kcal/d ($P < 0.01$) for men and 146 ± 78 kcal/d ($P < 0.001$) for women (12).

Gallagher et al’s observations show that the assumed organ-tissue-specific metabolic rate values, which are based largely on young adults, may not be applicable in the elderly. Two explanations for these findings are possible. First, the elderly may have a lower REE per unit cell mass for individual organs and tissues (ie, specific metabolic rate) than do young subjects. Second, the cellular fraction of organs and tissues may differ in young and older subjects. In support of the latter explanation, well established histologic changes in liver and other tissues show a relative loss of cellularity and an expansion of the extracellular compartments (13).

The hypothesis of the present study was that the lower than predicted REE observed in the elderly may be explained by a relative loss in organ-tissue cellularity. Currently, no in vivo methods are available for measuring both organ-tissue cell mass and the corresponding specific resting metabolic rates. In the present investigation, we derive a model for the age-related decline in cell mass and apply in vivo imaging and measurement

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methods to specifically explore the hypothesis that the age-related lowering of REE observed in the elderly can be accounted for by a loss of organ-tissue cell mass.

SUBJECTS AND METHODS

Study design and protocol

REE was measured by indirect calorimetry. Body cell mass (BCM) and the mass of each major organ and tissue were measured in vivo by using whole-body $^{40}$K counting and MRI, respectively. We then used currently available organ-tissue-specific resting metabolic rates (14) along with BCM and organ-tissue mass to model REE at the cellular body-composition level. We assume in this model that specific resting metabolic rates of individual cell categories are stable across the adult age years and that the age-related loss of cell mass is proportionally uniform across all organs and tissues. We compared REE estimates calculated by our model with those measured by indirect calorimetry.

On the first day, each subject completed a medical evaluation that included a physical examination and screening blood tests. Healthy free-living subjects without any diagnosed medical conditions and with normal thyroid hormone values were enrolled in the study. Total body potassium (TBK) and FFM were measured with whole-body $^{40}$K counting and dual-energy X-ray absorptiometry (DXA) systems, respectively. On the second day, liver, brain, kidney, skeletal muscle, and adipose tissue volumes were measured by using regional and whole-body MRI. Left ventricular heart volume was quantified by echocardiography. Whole-body REE was measured on the third evaluation day by indirect calorimetry after the subjects had fasted overnight.

REE prediction model

Whole-body REE can be expressed as the sum of energy expended by individual organs and tissues. The general REE model at the organ-tissue level is:

$$\text{REE} = \sum (J_i \times \text{ffcm}_i)$$

(1)

where REE is in kcal/d, $J_i$ is the specific resting metabolic rate of individual organs and tissue (in kcal · kg⁻¹ · d⁻¹), $i$ is a specific organ-tissue compartment ($i = 1, 2, \ldots, n$), and $M_i$ is individual organ-tissue mass (in kg). $M_i$ can be calculated as $M_i = V_i \times d_i$, where $V_i$ is the organ-tissue volume and $d_i$ is organ-tissue density.

The reference man’s $K_i$ values ($K_{ri}$) for Equation 1 are based on experimental values reported by Elia (14, 15) as follows (in kcal · kg⁻¹ · d⁻¹): liver, 200; brain, 240; heart and kidney, 440; skeletal muscle, 13; adipose tissue, 4.5; and residual tissues, 12. Accordingly, Gallagher et al (9) derived an REE prediction formula at the organ-tissue level:

$$\text{REE} = 200M_{\text{liver}} + 240M_{\text{brain}} + 440M_{\text{heart}} + 440M_{\text{kidneys}} + 13M_{\text{SM}} + 4.5M_{\text{AT}} + 12M_{\text{Res}}$$

(2)

where REEp is predicted REE (in kcal/d), $M_{\text{SM}}$ is skeletal muscle mass, $M_{\text{AT}}$ is adipose tissue mass, and $M_{\text{Res}}$ is residual mass, all expressed in kg. Residual tissues include skeleton, blood, skin, connective tissue, gastrointestinal tract, lung, spleen, and other components present in small amounts. Residual mass in this model is calculated as body weight minus the sum of liver, brain, heart, kidneys, skeletal muscle, and adipose tissue mass.

Each organ and tissue consists of fat, fat-free cell mass (ffcm), extracellular fluid, and extracellular solids (16). Of the 4 constituents, only ffcm consumes oxygen and produces heat (17). Whole-body REE can thus be expressed as the sum of energy expended by total ffcm at rest,

$$\text{REE} = \sum (J_i \times \text{ffcm}_i)$$

(3)

where $J_i$ is the specific resting metabolic rate of the individual cell category (in kcal · kg⁻¹ · d⁻¹), ffcm is the ffcm of an individual cell category (in kg), and $i$ is the specific cell category of interest ($i = 1, 2, \ldots, n$). Equation 3 is the general cellular-level model for whole-body REE. At present, no methods are available for estimating the fraction of individual organs and tissues as cells in vivo and corresponding $J_i$ values. We therefore sought an alternative working model by which to predict whole-body REE at the cellular level.

Each organ and tissue consists of fat and fat-free mass (ffm), and ffm represents the sum of ffcm and extracellular fluid and solids. The relation between ffcm, and organ-tissue mass (ie, $M_i$) can be expressed as

$$\text{ffcm} = M_i \times (\text{ffm} / M_i) \times (\text{ffcm} / \text{ffm})_i$$

(4)

where $(\text{ffm} / M_i)$ is the fraction of individual organ-tissue mass as ffm, and $(\text{ffcm} / \text{ffm})_i$ is the fraction of ffm as ffcm for an individual organ and tissue.

Of the 4 components of each organ and tissue, ffcm is the only one that relates to energy metabolism. The relation between $J_i$ and $K_i$ is thus

$$J_i = K_i [(\text{ffm} / M_i) \times (\text{ffcm} / \text{ffm})_i]$$

(5)

A similar formula can be written for the relation between $J_{ri}$ and $K_{ri}$ in a reference man:

$$J_{ri} = K_{ri} [(\text{ffm} / M_{ri}) \times (\text{ffcm} / \text{ffm})_{ri}]$$

(6)

where $(\text{ffm} / M_{ri})$ is the fraction of individual organ-tissue mass as ffm for the reference man and $(\text{ffcm} / \text{ffm})_i$ is the fraction of ffm as ffcm for the individual organ-tissue in reference man (Table 1).

Assuming $J_i$ values are stable within and across healthy adults (ie, $J_i = J_{ri}$), we can use Equation 6 to estimate $J_i$ by use of the following formula:

$$J_i = K_{ri} [(\text{ffm} / M_{ri}) \times (\text{ffcm} / \text{ffm})_{ri}]$$

(7)

Inserting Equations 4 and 7 into Equation 3, the cellular-level REE prediction model can be converted to

$$\text{REE} = \sum (K_{ri} \times M_i \times (\text{ffm} / M_i) \times (\text{ffcm} / \text{ffm})_i) [(\text{ffm} / M_{ri}) \times (\text{ffcm} / \text{ffm})_{ri}]$$

(8)

In the present study, organ and tissue volumes were assessed by MRI, and visible adipose tissue areas within organ-tissue cross-sectional scans were removed. We therefore assume $(\text{ffm} / M_i)$ to be stable across healthy adults [ie, $(\text{ffm} / M_i) = (\text{ffm} / M_{ri})$], and thus Equation 8 can be simplified to

$$\text{REE} = \sum (K_{ri} \times M_i \times (\text{ffcm} / \text{ffm})_i)$$

(9)

In Equation 9, the terms $(\text{ffcm} / \text{ffm})_i$ represent the fraction of individual fat-free organs and tissues as cell mass.
TBK measured by whole-body 40K counting [i.e., BCM (kg) FFM]. BCM contains almost all body potassium, and the mean body cellularity of FFM in reference man.

The BCM is 32.9 kg (i.e., 0.0092 kg/mmol weighing 70 kg contains 140 g (3581 mmol) potassium and 56.7 kg FFM (15). The BCM is 23.5 kg (i.e., 0.0092 kg/mmol × 2558 mmol) and (BCM/FFM)R is thus equal to 23.5/42 = 0.56.

Similarly, a reference woman with 55 kg of body weight contains 100 g (2558 mmol) potassium and 42 kg FFM (15). The BCM is 23.5 kg (i.e., 0.0092 kg/mmol × 2558 mmol) and (BCM/FFM)R is thus equal to 23.5/42 = 0.56.

for a subject and for a reference man, respectively. Because (ffcm/ffm)R is constant and (fcfcm), may decrease during aging, the ratio of (fcfcm), to (fcfcm)R can be used as an index of an individual’s cellularity relative to reference man’s cellularity. We refer to this index as the relative cellularity of organs and tissues. We make an assumption that for each healthy subject, the relative cellularity of individual organs and tissues is equal to the relative cellularity of whole-body FFM, i.e.,

\[
\frac{(fcfcm/(fcfcm)R)}{(fcfcm/(fcfcm)R)} = \left(\frac{BCM/FFM}{(BCM/FFM)R}\right)
\]

(10)

where (BCM/FFM)R is the whole-body fraction of FFM as BCM for a reference man. Equation 9 can thus be further simplified to

\[
REEp = \left(\frac{BCM/FFM}{(BCM/FFM)R}\right) \times (K_M \times M_{f})
\]

(11)

Equation 11 is the cellular-level REE prediction model applied in the present study, where BCM/FFM is the measured whole-body cellularity of FFM, and (BCM/FFM)R is the calculated whole-body cellularity of FFM in reference man.

Compared with the organ-tissue-level prediction model (Equation 1), the cellular-level prediction model adds a new variable: the whole-body fraction of FFM as BCM (i.e., BCM/FFM). BCM contains almost all body potassium, and the mean potassium concentration of BCM is relatively stable at 109.1 mmol/kg (18, 19). Whole-body BCM can thus be calculated from TBK measured by whole-body 40K counting [i.e., BCM (kg) = 0.0092 × TBK (mmol)]. A reference man aged 20–30 y and weighing 70 kg contains 140 g (3581 mmol) potassium and 56.7 kg FFM (15). The BCM is 32.9 kg (i.e., 0.0092 kg/mmol × 3581 mmol), and (BCM/FFM)R is thus equal to 32.9/56.7 = 0.58. Equation 11 can be simplified to

\[
REEp = \left(\frac{BCM/FFM}{0.58}\right) \times (K_M \times M_{f})
\]

(12)

Subjects

The subjects were a convenience sample of healthy free-living men and women recruited from among employees and persons residing in the New York City area who participated in earlier reported studies (9, 12). The studies were approved by the Institutional Review Board of St Luke’s–Roosevelt Hospital Center. All subjects gave written consent to participate.

REE measurement

REE was measured by using the Columbia Respiratory Chamber Indirect Calorimeter with the participants in a postabsorptive state. Details of the system design and calibration were reported previously (9).

Organ and tissue volumes

Whole-body MRI was applied for the measurements of 3 organs (liver, brain, and kidneys) and 2 tissue (skeletal muscle and adipose tissue) volumes. Subjects were placed on the 1.5-T scanner (6X Horizon; General Electric, Milwaukee, WI) platform with their arms extended above their heads. Protocol details were described previously (9). Briefly, liver and kidney images were produced by using an axial T1-weighted spin echo sequence with 5-mm slice thickness and no interslice gap. About 40 slices were acquired from the diaphragm to the base of the kidneys. Brain images (≈29) were generated by using a body coil with a fast-spin echo T2-weighted sequence and 5-mm contiguous axial images.

TABLE 1

<table>
<thead>
<tr>
<th>Organ</th>
<th>Mass (kg)</th>
<th>Potassium (mmol/kg)</th>
<th>(ffcm/ffm)R</th>
<th>(ffcm/ffm)</th>
<th>K_M (kcal/kg tissue⁻¹·d⁻¹)</th>
<th>J_M (kcal/kg cells⁻¹·d⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>1.8</td>
<td>64</td>
<td>0.91</td>
<td>0.63</td>
<td>200</td>
<td>350</td>
</tr>
<tr>
<td>Brain</td>
<td>1.4</td>
<td>77</td>
<td>0.89</td>
<td>0.79</td>
<td>240</td>
<td>340</td>
</tr>
<tr>
<td>Heart</td>
<td>0.33</td>
<td>56</td>
<td>0.90</td>
<td>0.57</td>
<td>440</td>
<td>860</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.31</td>
<td>49</td>
<td>0.95</td>
<td>0.47</td>
<td>440</td>
<td>980</td>
</tr>
<tr>
<td>SM</td>
<td>28</td>
<td>77</td>
<td>0.98</td>
<td>0.72</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>AT</td>
<td>15</td>
<td>8.2</td>
<td>0.20</td>
<td>0.38</td>
<td>4.5</td>
<td>60</td>
</tr>
<tr>
<td>Residual</td>
<td>23.16</td>
<td>46</td>
<td>0.98</td>
<td>0.43</td>
<td>12</td>
<td>29</td>
</tr>
<tr>
<td>Whole body</td>
<td>70</td>
<td>51</td>
<td>0.81</td>
<td>0.58</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The mass (M_i) and potassium contents ([P_i]) of individual organs and tissues were taken from reference man (15), as were the specific resting metabolic rate (K_M) of organs and tissues (3). Both (ffm/M_i)R and (bcf/mffm)R were calculated, and the J_M values were derived by using Equation 6. AT, adipose tissue; (ffcm/ffm)R, fraction of fat-free mass as cell mass of individual organs and tissues in reference man; (ffm/M_i)R, fraction of individual organ and tissue mass as fat-free mass in reference man; J_M, specific resting metabolic rate of individual cell category of reference man; residual, the difference between body weight and the sum of the 6 measured organs and tissues; SM, skeletal muscle.
Heart mass

Left ventricular mass was evaluated with a two-dimensionally guided M-mode echocardiogram (Hewlett-Packard 1500, Boise, ID) with a minimum of 5 cardiac cycles (9). Heart mass was calculated as 1.5 times left ventricular mass (21).

Total body fat and fat-free mass

Total body fat and FFM were measured with a DXA scanner (DPX, version 3.6 software; Lunar Radiation Corp, Madison, WI). The between-measurement technical error for FFM in the same person was 1.2%.

Total body potassium

The St Luke’s 4π whole-body counter was used to detect the natural 1.46 MeV γ-ray of subject $^{40}$K. The $^{40}$K raw counts collected over 9 min were adjusted for body size on the basis of an experimental $^{42}$K calibration equation (22). TBK mass was calculated as $^{40}$K/0.000118 (23). The current technical error in our laboratory for repeated phantom $^{40}$K counting is $±2.4%$. BCM was calculated from TBK as BCM (kg) = 0.0092 × TBK (mmol) (19).

Total body water

The deuterium ($^2$H$_2$O) dilution space was estimated with a precision of 1.2%. The deuterium dilution space was then converted into TBW mass (kg) by correcting for nonaqueous hydrogen exchange (0.96) and water density at 36 °C (0.9937 g/cm$^3$) (24).

Water distribution

Extracellular water (ECW, in kg) and intracellular water (ICW, in kg) were calculated from TBK (in mmol) and TBW (in kg) on the basis of the following simultaneous equations:

$$\text{TBK} = 152 \times \text{ICW} + 4 \times \text{ECW} \quad (13)$$

$$\text{TBW} = \text{ICW} + \text{ECW} \quad (14)$$

where 152 and 4 are intracellular and extracellular potassium concentrations (both in mmol/kg H$_2$O), respectively (25). ECW, ICW, and the ratio of ECW to ICW (E/I) can be calculated as

$$\text{ECW} = (152 \times \text{TBW} - \text{TBK})/148 \quad (15)$$

$$\text{ICW} = (\text{TBK} - 4 \times \text{TBW})/148 \quad (16)$$

$$E/I = (152 \times \text{TBW} - \text{TBK})/(\text{TBK} - 4 \times \text{TBW}) \quad (17)$$

Statistical analysis

Descriptive subject data are expressed as the group mean ± SD. Statistical significance was set at $P < 0.05$. The significance of body-composition and measured REE differences between men and women were evaluated by Student’s t test. The relation between measured and predicted REE (REEm – REEp) and age and between the fraction of FFM as BCM and age and sex were examined by using simple linear regression analysis and general linear models.

The cellular-level REE model was tested by examining the association between REEm and REEp with the use of simple linear regression analysis. We then explored for bias in the REEm and REEp relation by using the method reported by Bland and Altman (26). Finally, we explored the correlations between (REEm – REEp) and age for the whole group with linear regression. We then explored for bias in the REEm and REEp relation by using the method reported by Bland and Altman (26). Finally, we explored the correlations between (REEm – REEp) and age for the whole group with linear regression. We then explored for bias in the REEm and REEp relation by using the method reported by Bland and Altman (26). Finally, we explored the correlations between (REEm – REEp) and age for the whole group with linear regression. We then explored for bias in the REEm and REEp relation by using the method reported by Bland and Altman (26). Finally, we explored the correlations between (REEm – REEp) and age for the whole group with linear regression. We then explored for bias in the REEm and REEp relation by using the method reported by Bland and Altman (26). Finally, we explored the correlations between (REEm – REEp) and age for the whole group with linear regression. We then explored for bias in the REEm and REEp relation by using the method reported by Bland and Altman (26). Finally, we explored the correlations between (REEm – REEp) and age for the whole group with linear regression. We then explored for bias in the REEm and REEp relation by using the method reported by Bland and Altman (26). Finally, we explored the correlations between (REEm – REEp) and age for the whole group with linear regression.
TABLE 3

Subject cellular-level body-composition results.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>Total group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 17)</td>
<td>(n = 32)</td>
<td>(n = 49)</td>
</tr>
<tr>
<td>ECW (kg)</td>
<td>21.0 ± 3.0</td>
<td>17.6 ± 2.6</td>
<td>18.8 ± 3.2</td>
</tr>
<tr>
<td>ICW (kg)</td>
<td>24.9 ± 3.9</td>
<td>15.9 ± 2.4</td>
<td>19.0 ± 5.2</td>
</tr>
<tr>
<td>E/I</td>
<td>0.859 ± 0.151</td>
<td>1.117 ± 0.171</td>
<td>1.027 ± 0.205</td>
</tr>
<tr>
<td>BCM (kg)</td>
<td>35.5 ± 5.4</td>
<td>22.9 ± 3.4</td>
<td>27.3 ± 7.4</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>62.7 ± 7.4</td>
<td>45.2 ± 5.8</td>
<td>51.3 ± 10.7</td>
</tr>
<tr>
<td>BCM/FFM</td>
<td>0.565 ± 0.039</td>
<td>0.506 ± 0.029</td>
<td>0.527 ± 0.043</td>
</tr>
</tbody>
</table>

All values are x ± SD. Results are for 49 of 54 subjects. BCM, body cell mass; BCM/FFM, cell fraction of fat-free mass; ECW, extracellular water; E/I, ratio of extracellular to intracellular water; FFM, fat-free mass; ICW, intracellular water. Means for men and women were all significantly different, P < 0.001 (t test).

REE prediction by new model

The mean REEm was 1487 ± 294 kcal/d and REEp was 1501 ± 300 kcal/d with a nonsignificant mean difference (ie, REEm – REEp) of ~14 ± 117 kcal/d for the whole group of subjects. REEm was highly correlated with REEp (r = 0.92, P < 0.001). A Bland-Altman plot showed that there was no significant trend (r = 0.053, P > 0.50) between measured and predicted REE difference versus the average of REEm and REEp (Figure 3). The difference between REEm and REEp is plotted against age for all subjects in Figure 4, which shows that the measured and predicted REE difference is not significantly associated with age.

DISCUSSION

One of the primary aims of energy metabolism research is to understand the inherent relations between REE and body composition. Several studies have investigated whether the lower REE in the elderly can be accounted for by aging-related changes in body composition (12). However, the previous organ-tissue-level model does not explain the lower REE observed in the elderly age. Therefore, the present study, we proposed and evaluated a cellular-level REE prediction model. Although Equation 3 is theoretically correct, this model is currently impractical to apply because of the technical difficulties in measuring cell mass and specific resting metabolic rates of individual cell groups. Equation 12, although based on simplifications and assumptions, may be the only currently operable approach for predicting REE at the cellular level.
Because specific resting metabolic rates of individual cell groups (ie, \( J_i \)) were assumed to be stable across the adult age span, there were 2 possible outcomes of the present study. The first possibility was that the new model would accurately predict REE, which would suggest that \( J_i \) values are constant from young to old age and that the decline in the fat-free cell fraction of FFM is responsible for the lower REE observed in the elderly. The second possibility was that REE in the elderly would still be overpredicted after the cellular level of body composition was taken into account; this finding would support the conclusion that changes in both \( J_i \) and the cell fraction of FFM account for the lower REE in the elderly. The results of the present study are consistent with the first alternative, ie, that the lower REE observed in elderly subjects is adequately explained by the lower cell fraction of FFM.

**FIGURE 2.** Fraction of fat-free mass (FFM) as body cell mass (BCM) versus age for men (○) and women (○). The linear regression line (solid line) for all subjects (BCM/FFM = 0.573 − 0.001 × age; \( r = −0.48, P < 0.001; n = 54 \)) and 95% CIs (dashed line) are shown.

**FIGURE 3.** The difference between measured and predicted whole-body resting energy expenditure (REEm – REEp) versus the mean of REEm and REEp for men (○) and women (○) or all subjects (\( y = 17.7 − 0.02x; r = 0.053, P > 0.50; n = 54 \)). REEp was calculated according to the cellular-level model (Equation 12). The regression line, zero difference line, and the lines representing 2 SDs for the differences (220, −248 kcal/d; indicated by the upper and lower lines) are shown.
accurate value of \((\text{BCM}/\text{FFM})_R\) can be calculated as a function of invasive, in vivo methods for measuring specific resting metabolic rates of individual cell groups, noninvasive organs and tissues are documented for a reference man (15), and the specific resting metabolic rates of organs and tissues are also documented \((K_i)\) (3). Both \((\text{ffm}/M)_R\) and \((\text{bcm}/\text{ffm})_R\) could thus be calculated and the \(K_i\) values derived by using Equation 6 (Table 1). Although there is a need to measure the specific resting metabolic rates of individual cell groups, noninvasive, in vivo methods for measuring \(J_i\) values remain technically demanding (29, 30). As the most advanced techniques become available [e.g., methods based on magnetic resonance spectroscopy (MRS) and positron emission tomography (PET)] in vivo quantification of specific resting metabolic rates of individual cell groups may be possible.

Whole-body BCM does not remain a fixed fraction of FFM, but decreases with greater age (31, 32). In the present study, we present additional evidence that supports a decline in the cell mass fraction of FFM. The ratio of ECW to ICW, which is an index of the FFM cell fraction, was significantly correlated with the potassium and FFM content of individual organs and tissues, lower in the men aged 70 y than for the men and women aged 23–39 y (Table 3). Observations suggest that the cell fractions of individual organs and tissues are smaller in older subjects than in younger ones.

In Equation 12, simplified values were used for the \((\text{BCM}/\text{FFM})_R\) for the reference man (ie, 0.58) and woman (ie, 0.56). An accurate value of \((\text{BCM}/\text{FFM})_R\) can be calculated as a function of the potassium and FFM content of individual organs and tissues, \((\text{BCM}/\text{FFM})_R = [(0.0092 \times \text{TBK})/\text{FFM}]_R = 0.0092 \times \Sigma ([\text{ffm}/M]_i \times M_i)/\Sigma ([\text{ffm}/M]_R \times M_i)\) (18) where 0.0092 is the coefficient for conversion of TBK (in mmol) to BCM (in kg) reported by Wang et al (20), \([P]_R\) is the potassium content (in mmol/kg) of individual organs and tissues in the reference man, and \((\text{ffm}/M)_R\) is the FFM content of individual organs and tissues in the reference man (Table 1). Because an individual subject may have organ and tissue mass proportions of FFM that differ from those in the reference man, the calculation of cell mass decline with age can be made more accurate by using a relative cellularity factor corrected for variation in organ proportions [ie, an individually adjusted \((\text{BCM}/\text{FFM})_R\)]. Specifically,

\[
(\text{BCM}/\text{FFM})_R = 0.0092 \times \left(64M_{ \text{Liver}} + 77M_{ \text{Brain}} + 56M_{ \text{Heart}} + 49M_{ \text{Kidneys}} + 77M_{ \text{SM}} + 8.2M_{ \text{AT}} + 46M_{ \text{Res}}\right)/(0.91M_{ \text{Liver}} + 0.89M_{ \text{Brain}} + 0.90M_{ \text{Heart}} + 0.95M_{ \text{Kidneys}} + 0.98M_{ \text{SM}} + 0.20M_{ \text{AT}} + 0.98M_{ \text{Res}})
\]

Equation 19 is complex, however, and, in this subject group, the increase in accuracy (0.580 ± 0.015 versus 0.58 for men and 0.563 ± 0.012 versus 0.56 for women) was small. Therefore we use simply 0.58 for men and 0.56 for women as the value of \((\text{BCM}/\text{FFM})_R\) in Equation 11.

Several limitations of the current study are worthy of mention. In the present investigation, a simplifying assumption was made that the relative cellularity of various organs and tissues decreases during aging at the same rate as the relative cellularity of whole-body FFM. The relative cellularity of FFM was 12.5% lower in the men aged ≥70 y and 10.4% lower for the women aged ≥70 y than for the men and women aged 23–39 y (Table 3). We made an assumption that the relative cellularity for each organ and tissue was also 12.5% and 10.4% lower in the elderly men and women, although this is a simplification for the purpose of model development. Advanced methods will need to be developed to accurately measure the cellular fraction of individual organs and tissues in vivo.

**FIGURE 4.** The difference between measured and predicted whole-body resting energy expenditure (REEm – REEp) versus age for men (○) and women (●). The linear regression line (solid line) for all subjects [(REEm – REEp) = −16.2 ± 0.05 × age; \(r = 0.009, P > 0.50; n = 54\) and 95% CIs (dashed lines) are shown. REEp was calculated according to the cellular-level model (Equation 12).
When this study was carried out, the only method available for measuring heart mass at our center was echocardiography. However, echocardiography actually measures left ventricular mass and not total heart mass. Compared with autopsy data, echocardiography underestimates total heart mass by 50% (21). In the present study, we thus calculated heart mass as 1.5 × left ventricular mass. More recently, we replaced echocardiography as a means of measuring heart mass with cardiac gated MRI.

The number of evaluated subjects was small in the present study. There were only 11 elderly subjects in the age range of 70–88 y and no subjects between the ages of 60 and 69 y. More elderly subjects are thus needed to further confirm the new REE model. Moreover, predicted REE based on organ and tissue mass alone is significantly smaller (~25%) than the measured REE for children (33). Although the new model works well in elderly subjects, other factors may influence REE during growth and our model is therefore inappropriate for use in children.

In conclusion, previous studies showed that the application of specific metabolic rate coefficients to organ and tissue mass data alone cannot entirely account for the lower REE observed in elderly adults. In the present study, we modified the existing organ-tissue-level REE model and improved REE prediction by introducing an additional body-composition factor, the cellular fraction of FFM. Further studies and new methods are needed to evaluate actual organ- and tissue-specific metabolic rates in vivo. ZMW and SBH were responsible for model development, data analysis, and manuscript writing. SH was responsible for statistical analysis and manuscript writing. WS was responsible for model development. DG was responsible for data collection and manuscript writing. No author had a conflict of interest in any company or organization sponsoring this study.

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