Three-compartment model: critical evaluation based on neutron activation analysis

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Silva, Analiza M., Wei Shen, ZiMian Wang, John F. Aloia, Miriam E. Nelson, Steven B. Heymsfield, Luis B. Sardinha, and Stanley Heshka. Three-compartment model: critical evaluation based on neutron activation analysis. Am J Physiol Endocrinol Metab 287: E962–E969, 2004. First published June 8, 2004; doi:10.1152/ajpendo.00104.2004.—There is renewed interest in Siri’s classic three-compartment (3C) body composition model, requiring body volume (BV) and total body water (TBW) estimates, because dual-energy X-ray absorptiometry (DEXA) and in vivo neutron activation (IVNA) systems cannot accommodate subjects with severe obesity. However, the 3C model assumption of a constant ratio (α) of mineral (M) to total body protein (TPBPro) and related residual mass density (DRES) based on cadaver analyses might not be valid across groups differing in sex, race, age, and weight. The aim of this study was to derive new 3C model coefficients in vivo and to compare these estimates to those derived by Siri. Healthy adults (n = 323) were evaluated with IVNA and DEXA and the measured components used to derive α and DRES. For all subjects combined, values of α and DRES (means ± SD, 0.351 ± 0.043; 1.565 ± 0.023 kg/l) were similar to Siri’s proposed values of 0.35 and 1.565 kg/l, respectively. However, α and DRES varied significantly as a function of sex, race, weight, and age. Expected errors in percent body fat arising by application of Siri’s model were illustrated in a second group of 264 adults, including some whose size exceeded DEXA limits but whose BV and TBW had been measured by hydrodensitometry and 2\textsuperscript{H}O dilution, respectively. Extrapolation of predictions by newly developed models to very high weights allows percent fat error estimation when Siri’s model was applied in morbidly obese subjects. The present study results provide a critical evaluation of potential errors in the classic 3C model and present new formulas for use in selected populations.

Although approach of Behnke et al. (2) filled a critical methodology gap for body fat measurement, workers in the following two decades noted model concerns, notably the assumption that FFM density is constant across all subjects in health and disease, including in patients with severe obesity (8). The FFM component at the molecular body composition level includes total body water (TBW), protein (TPBPro), soft tissue minerals (Ms), bone minerals (Mo), and glycogen (G) (25). Any actual subject differences in the proportions of these components from those assumed stable on the basis of cadaver studies by early two-component model developers (2, 3) will lead to fat and FFM estimation errors.

Siri in 1956 (22) and later in 1961 (23) derived a three-component (3C) model that accounted for variation in subject hydration by adding a TBW estimate to Behnke’s two-component model (2). On the basis of data available at the time for five chemically analyzed human cadavers (11, 16, 26), Siri assumed that FFM consisted of two molecular level components, TBW, and a combined TBPro and total mineral (M, i.e., the sum of Ms and Mo) residual component. To complete the model, Siri suggested an M-to-TBPro ratio (i.e., α) of 0.35, as estimated from the five cadavers, with a corresponding density of 1.565 kg/l.

In recent years, Siri’s 3C model (23) has been supplanted by more complex four- and six-component models as estimation of Ms and Mo became possible with in vivo neutron activation (IVNA) analysis (4, 6) and dual-energy X-ray absorptiometry (DEXA) (19). However, most DEXA and IVNA systems cannot accommodate subjects with severe or morbid obesity, leaving underwater weighing or the recently introduced airplethysmography methods for body volume measurement, along with TBW measurement by isotope dilution, as viable means by which to quantify fat and FFM. Therefore, renewed interest is now directed to Siri’s 3C model with the rising prevalence of obesity (29). This led us in the current study to critically evaluate Siri’s 3C model (23) as it applies across sex, age, weight, and racial groups. We specifically focused our attention on the assumed value of α and the related density of the combined compartment including M, TBPro, and G. IVNA analysis and DEXA techniques, unavailable during Siri’s era, allowed us to evaluate Ms, Mo, TBPro, and G in a large sample of healthy adults.

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METHODS

Protocol and Subjects

The primary aim of this study was to compare the classical 3C model α value (0.35) and related density (1.565 kg/l) proposed by Siri with the corresponding estimates provided by combined IVNA and DEXA measurements. After the initial health examination of each subject, a DEXA scan was performed at St. Luke's-Roosevelt Hospital in New York City. On the next study day, subjects underwent delayed-γ and prompt-γ IVNA analysis and whole body 40K counting at Brookhaven National Laboratory (BNL) in Upton, Long Island.

Subjects were a convenience sample of 323 healthy adults participating in other unrelated investigations. A physical examination and routine blood studies indicated that each of these individuals was in good health. The sex and racial distribution of this sample was dictated by the original planned studies.

In a second phase of our study, we examined potential biological errors inherent in the Siri formula compared with the new models developed in the initial study group. These errors were modeled for illustrative purposes in a second convenience sample of 293 healthy adults who had body volume and TBW measured by underwater weighing and deuterium dilution (H2O2), respectively, on the same day. These subjects participated in other ongoing investigations (18) and did not complete neutron activation analysis studies. The sample includes subjects at the extreme upper range of body weight, whose size necessitates the development and improvement of alternative practical evaluation methods. The investigation was approved by the Institutional Review Boards of St. Luke's-Roosevelt Hospital and BNL.

Body Composition Measurements

TBK. TBK was estimated from the measured 1.46 MeV γ-ray decay of naturally occurring 40K, as TBK = 40K/0.000118 (17). Naturally occurring 40K was determined with the BNL whole body counter, which has a between-measurement coefficient of variation (CV) of 1% (4, 5).

TBW. TBW, expressed in kilograms, was measured by deuterium dilution corrected for 4% isotope exchange and water density at 36°C (20).

BV. BV, expressed in liters, was determined by underwater weighing. Body weight during submersion was recorded by platform force transducers during a 5-s maximal expiration. After a series of practice trials, 10 runs were performed, and the density results were averaged. Corrections in density were made for residual lung volume by using a closed-circuit oxygen-dilution system described by Wilmore (27). Residual volume was measured immediately after the underwater weighing procedure. The CV between days for body volume technique is 1.7% body fat on the basis of repeated studies in five weight-stable individuals in this laboratory.

General 3C Model Derivation

Body minerals were quantified from total body amounts of Ca, K, Na, and Cl by a combination of whole body 40K counting and delayed-γ IVNA methods, and total body bone mineral (Mo) was quantified from DEXA. Specifically, soft tissue mineral (Ms) was calculated from TBK, TBNa, TBCl, and TBCa (all in kg) as (25, 13)

\[
\text{Ms} = 2.76 \times \text{TBK} + \text{TBNa} + 1.43 \times \text{TBCl} - 0.038 \times \text{TBCa} \tag{1}
\]

Total body mineral (M) was calculated as

\[
M = \text{Mo} + \text{Ms} \tag{2}
\]

Total body protein was calculated from TBN measured in vivo with prompt-γ neutron activation analysis (7, 15) as TBPro = 6.25 × TBN. Glycogen (G) was calculated from TBPro as G = 0.044 × TBPro (24).

According to Eq. 2, the M/TBPro ratio was calculated as

\[
\frac{M}{\text{TBPro}} = \alpha = \frac{\text{Mo} + \text{Ms}}{\text{TBPro}} \tag{3}
\]

The residual mass (RES) is the sum of soft tissue and bone minerals, protein, and glycogen mass:

\[
\text{RES} = \text{Mo} + \text{Ms} + \text{TBPro} + G \tag{4}
\]

Dividing by the respective densities,

\[
\frac{\text{RES}}{D_{\text{RES}}} = \frac{\text{Mo}/2.982 + \text{Ms}/3.317 + \text{TBPro}/1.34 + G/1.152}{8} \tag{5}
\]

where DRES is the residual mass density. When Eq. 5 is considered, DRES can be expressed as

\[
D_{\text{RES}} = 1/(f/\text{Mo}/2.982 + f/\text{Ms}/3.317 + f/\text{TBPro}/1.34 + f/G/1.152) \tag{6}
\]

where f/Mo, f/Ms, f/TBPro, and f/G are the fractions of residual mass as bone mineral, soft tissue mineral, protein, and glycogen, respectively.

Body mass (BM) and volume (BV) models can be written as

\[
\text{BM} = \text{FM} + \text{TBW} + \text{RES} \tag{7}
\]

\[
\text{BV} = \text{FM}/0.9007 + \text{TBW}/0.9937 + \text{RES}/D_{\text{RES}} \tag{8}
\]

where FM is fat mass. By resolving the simultaneous Eqs. 7 and 8, a 3C fat model can be derived as follows:

\[
\text{FM} = \left[ \frac{\text{BV} - (1.0063 - 1/D_{\text{RES}}) \times \text{TBW} - \text{BM}/D_{\text{RES}}}{1.1102 - 1/D_{\text{RES}}} \right] \tag{9}
\]

We derived a general 3C model based on measurable BM, BV, TBW, and DRES. This allowed us to examine the effects of varying mineral and protein proportions on estimates of FM.
The general 3C model is

\[ FM = C_1 \times BV - C_2 \times TBW - C_3 \times BM \]  

(10)

where \( FM \) is in kilograms, \( BV \) is in liters, \( TBW \) is in kilograms, and \( BM \) is in kilograms. Each coefficient can be calculated from the following equations:

\[ C_1 = \frac{D_{\text{RES}}}{1.1102 \times D_{\text{RES}} - 1} \]  

(11)

\[ C_2 = \frac{1.0063 \times D_{\text{RES}} - 1}{1.1102 \times D_{\text{RES}} - 1} \]  

(12)

\[ C_3 = \frac{1}{1.1102 \times D_{\text{RES}} - 1} \]  

(13)

**Updated Siri 3C Model**

Siri combined BM, BV, and TBW estimates in developing his 3C model (23). The model requires density estimates for the three components: fat, water, and residual mass. The original Siri 3C equation reported in 1961 (23) (\( FM = 2.118 \times BV - 0.780 \times TBW - 1.354 \times BM \)) uses a value of 0.9000 kg/l for the density of fat and 0.9933 kg/l for the density of water at 37°C. Although body core temperature approximates 37°C, the average body temperature under basal conditions in a comfortable environment is 1–2°C lower (28). We therefore used 0.9007 and 0.9937 kg/l, respectively, for the densities of fat and water at 36°C (28). We adjusted Siri’s original 3C model (23) accordingly:

\[ FM = 2.122 \times BV - 0.779 \times TBW - 1.356 \times BM. \]  

(14)

This revised equation was used in place of Siri’s 1961 equation (23).

**Statistical Methods**

All group results are expressed as means ± SD. Analyses were carried out using the statistical program SPSS version 11.5 (SPSS, 2002).

The simple linear correlations between M and TBPro were examined, and the group mean TBPro and \( D_{\text{RES}} \) residual mass density values were compared between men and women. One-sample t-tests were used to compare the mean densities of residual mass and the \( \alpha \) values between subjects in the present study and the mean values for subjects reported by Siri (23) (1.565 kg/l and 0.35). Independent sample t-tests were used to compare the mean \( D_{\text{RES}} \) across sex and racial groups.

**RESULTS**

**Subject Characteristics**

Three hundred and twenty-three subjects, 293 females and 30 males, underwent the study protocol. From the female sample, 216 were Caucasian and 77 were African-American. In the male sample, 6 were Caucasians, 13 were African-American, 4 were Asians, and 7 were Hispanics. Subject characteristics for the model development sample are presented in Table 1. The table provides separate information on the Caucasian and African-American female sample, in addition to pooled values for all females combined. The males are presented as a single group due to its smaller size and a small number of subjects in each racial group.

The subjects ranged in weight from a low of 44.1 kg to a high of 96.0 kg, with an overall body mass index (BMI) (mean ± SD and range) of 24.9 ± 3.8 and 18.1–36.1 kg/m², respectively. The group as a whole was 50.8 ± 13.2 yr of age, with a range of 23–90 yr.

The model evaluation sample consisted of 264 subjects: 190 females (166 Caucasian and 24 African-American) and 74 males (31 Caucasians, 19 African-Americans, 17 Asians, 7 Hispanics). The characteristics of subjects in this group are presented for Caucasian and African-American females and pooled males in Table 2. The subjects in the evaluation sample

**Table 1. Subject characteristics and body composition results**

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>Females</th>
<th>Total</th>
<th>Total Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>C</td>
<td>AA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age, yr</td>
<td>30</td>
<td>216</td>
<td>77</td>
<td>293</td>
</tr>
<tr>
<td></td>
<td>Weight, kg</td>
<td>49.1 ± 17.9</td>
<td>53.5 ± 12.3</td>
<td>44.2 ± 11.1</td>
<td>51.1 ± 12.6</td>
</tr>
<tr>
<td></td>
<td>Height, cm</td>
<td>172.8 ± 8.3</td>
<td>163.2 ± 6.7</td>
<td>163.6 ± 5.7</td>
<td>163.3 ± 6.4</td>
</tr>
<tr>
<td></td>
<td>BMI, kg/m²</td>
<td>25.0 ± 2.8</td>
<td>24.5 ± 3.7</td>
<td>25.6 ± 4.1</td>
<td>24.8 ± 3.8</td>
</tr>
<tr>
<td></td>
<td>TBN, kg</td>
<td>1.76 ± 0.28</td>
<td>1.40 ± 0.14</td>
<td>1.48 ± 0.19</td>
<td>1.42 ± 0.16</td>
</tr>
<tr>
<td></td>
<td>TBCa, g</td>
<td>892.7 ± 135.2</td>
<td>654.8 ± 98.6</td>
<td>728.1 ± 83.4</td>
<td>674.1 ± 100.0</td>
</tr>
<tr>
<td></td>
<td>TBNa, g</td>
<td>81.1 ± 10.2</td>
<td>63.6 ± 6.5</td>
<td>67.0 ± 5.5</td>
<td>64.5 ± 6.4</td>
</tr>
<tr>
<td></td>
<td>TBCl, g</td>
<td>63.4 ± 9.5</td>
<td>68.1 ± 13.4</td>
<td>71.3 ± 12.4</td>
<td>69.0 ± 13.2</td>
</tr>
<tr>
<td></td>
<td>TBK, g</td>
<td>143.1 ± 28.7</td>
<td>102.4 ± 13.0</td>
<td>112.4 ± 12.2</td>
<td>105.1 ± 13.5</td>
</tr>
<tr>
<td></td>
<td>TBPro, kg</td>
<td>11.00 ± 1.72</td>
<td>8.74 ± 0.90</td>
<td>9.27 ± 1.21</td>
<td>8.88 ± 1.02</td>
</tr>
<tr>
<td></td>
<td>Glycogen, kg</td>
<td>0.484 ± 0.076</td>
<td>0.385 ± 0.040</td>
<td>0.408 ± 0.053</td>
<td>0.391 ± 0.044</td>
</tr>
<tr>
<td></td>
<td>Mo, kg</td>
<td>3.109 ± 0.543</td>
<td>2.598 ± 0.443</td>
<td>3.014 ± 0.447</td>
<td>2.707 ± 0.480</td>
</tr>
<tr>
<td></td>
<td>Ms, kg</td>
<td>0.533 ± 0.024</td>
<td>0.421 ± 0.049</td>
<td>0.451 ± 0.056</td>
<td>0.429 ± 0.050</td>
</tr>
<tr>
<td></td>
<td>( \alpha )</td>
<td>0.333 ± 0.045†</td>
<td>0.346 ± 0.028†</td>
<td>0.375 ± 0.036‡</td>
<td>0.353 ± 0.042*</td>
</tr>
<tr>
<td></td>
<td>( D_{\text{RES}} ), kg/l</td>
<td>1.555 ± 0.024‡</td>
<td>1.562 ± 0.022‡</td>
<td>1.578 ± 0.019‡</td>
<td>1.566 ± 0.023*</td>
</tr>
</tbody>
</table>

Values are means ± SD. AA, African-American; C, Caucasian; BMI, body mass index; M/TBPro, ratio mineral to protein; \( n \), number of subjects; TBCa, total body calcium; TBCl, total body chlorine; TBK, total body potassium; TBN, total body nitrogen; TBNa, total body sodium; TBPro, total body protein; Mo, bone mineral; Ms, soft tissue mineral; \( D_{\text{RES}} \), residual mass density. †Significant difference between males and females (\( P < 0.05 \)); ‡significantly different from the proposed Siri (23) density of mineral plus protein, 1.565 kg/l (\( P < 0.05 \)); §significant difference between AA and C females (\( P < 0.05 \)).
Table 2. Physical characteristics and body composition results from the independent validation sample

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>F</th>
<th>AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>74</td>
<td>166</td>
<td>24</td>
</tr>
<tr>
<td>Age, yr</td>
<td>39.0 ± 17.1</td>
<td>41.1 ± 12.2</td>
<td>47.4 ± 14.0</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78.8 ± 12.8</td>
<td>75.3 ± 12.4</td>
<td>75.3 ± 15.1</td>
</tr>
<tr>
<td>Height, cm</td>
<td>176.9 ± 6.8</td>
<td>164.4 ± 6.6</td>
<td>163.7 ± 8.3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.1 ± 3.5</td>
<td>28.9 ± 4.7</td>
<td>28.1 ± 5.2</td>
</tr>
<tr>
<td>TBW, kg</td>
<td>45.9 ± 6.9</td>
<td>32.7 ± 3.9</td>
<td>35.1 ± 3.7</td>
</tr>
<tr>
<td>BV, l</td>
<td>75.1 ± 12.7</td>
<td>74.7 ± 13.2</td>
<td>74.1 ± 16.1</td>
</tr>
<tr>
<td>D_res, kg/l</td>
<td>1.565 ± 0.013</td>
<td>1.565 ± 0.012</td>
<td>1.616 ± 0.015</td>
</tr>
<tr>
<td>%FM Siri-3C</td>
<td>20.80 ± 7.30</td>
<td>40.15 ± 7.40</td>
<td>35.31 ± 9.90</td>
</tr>
<tr>
<td>%FM Adjusted-3C</td>
<td>20.77 ± 7.40</td>
<td>40.15 ± 7.37</td>
<td>35.97 ± 9.69</td>
</tr>
<tr>
<td>%FM Differences-3C</td>
<td>-0.04 ± 0.23</td>
<td>-0.02 ± 0.18</td>
<td>0.66 ± 0.13</td>
</tr>
</tbody>
</table>

Values are means ± SD. BV, body volume; %FM, percent fat mass; 3C, 3-compartment body composition model; TBW, total body water. *Significant difference between males and females ($P < 0.05$). †Significant difference between AA and C females ($P < 0.05$); ‡Significantly different from the proposed Siri (23) density of mineral plus protein, 1.565 kg/l ($P < 0.05$); §Significantly different from 0 ($P < 0.05$).

ranged in weight from a low of 44.0 to a high of 107.9 kg, with a BMI mean and range of 27.8 ± 4.7 and 17.7–41.3 kg/m², respectively. The age of this sample was 41.1 ± 13.5 yr, with a range of 18–88 yr.

**Ratio of Mineral to Protein**

Total body M was highly correlated with TBPro, accounting for 52.1 and 50.0% of the variation between individuals in M for the males ($P < 0.001$) and females ($P < 0.001$), respectively. The value for $\alpha$ of 0.351 ± 0.043 for the whole sample matched closely Siri’s proposed $\alpha$ value of 0.35 ($P = 0.549$) and did not differ significantly from this value in the pooled female sample ($P = 0.174$) or in the sample of Caucasian females alone ($P = 0.116$) (Table 1). However, a lower mean $\alpha$ was observed in the male sample (0.333 ± 0.045, $P = 0.044$), and a higher $\alpha$ (0.375 ± 0.036, $P < 0.001$) was present in the African-American females compared with Siri’s $\alpha$ value of 0.35. Four of the cadavers reported by Siri (22, 23) were males, and one was a female.

The value of $\alpha$ varied significantly with age and weight among the groups (Fig. 1). The value of $\alpha$ significantly increased with weight in the male and African-American female samples ($r = 0.37, P = 0.045$; $r = 0.30, P = 0.007$) but not in the Caucasian females ($r = 0.12, P = 0.082$). The $\alpha$ value was significantly lower with greater age in the Caucasian females ($r = -0.42, P < 0.001$) but not in the males and African-American females ($r = -0.10, P = 0.588$ and $r = 0.11, P = 0.332$, respectively).

$D_{RES}$

**Propagated measurement error.** In the present study, we selected IVNA-estimated Ms, TBPro, and G as the criteria, because measurement precision is high for TBK, TBNa, TBCl, and TBCa. The error associated with measurement of the IVNA model components ($\sigma_{Ms}$) can be estimated for the healthy subjects by assuming an average body composition, as

Fig. 1. Ratio of mineral (M) to protein (TBPro) (i.e., $\alpha$) vs. independent variables of age and weight for males, Caucasian females ($\square$), and African-American females ($\bullet$).
shown in Table 1, and measurement precisions as stated in
METHODS. Accordingly,
\[
\sigma_{\text{Mo}}^2 = (2.76 \times 10.86 \times 0.010)^2 + (1 \times 0.066 \times 0.015)^2 \\
+ (1.43 \times 0.0685 \times 0.016)^2 \\
+ (0.038 \times 0.6944 \times 0.017)^2 = 0.00001262 \text{ kg}^2
\]
\[
\sigma_{\text{TBPro}}^2 = (6.25 \times 1.450 \times 0.028)^2 = 0.0644 \text{ kg}^2
\]
\[
\sigma_{\text{Gi}}^2 = (0.275 \times 1.450 \times 0.028)^2 = 0.0001 \text{ kg}^2
\]
The error associated with measurement of the DEXA com-
ponents (\(\sigma_{\text{Mo}}\)) can be estimated as follows:
\[
\sigma_{\text{Mo}}^2 = (1 \times 2.745 \times 0.013)^2 = 0.0013 \text{ kg}^2
\]
For the final residual mass, the propagation of error would be:
\[
\sigma_{\text{Res}}^2 = \sigma_{\text{Mo}}^2 + \sigma_{\text{Ms}}^2 + \sigma_{\text{TBPro}}^2 + \sigma_{\text{Gi}}^2
\]
\[
= 0.0658 \text{ kg}^2, (\sigma_{\text{Res}} = \sim 257 \text{ g}).
\]
In vivo observations. The D\(_{\text{RES}}\) (Table 1) matched closely
Siri’s (23) proposed value of 1.565 kg/l for the whole sample
(1.565 \pm 0.023 kg/l) and for the pooled female subjects
(1.566 \pm 0.023 kg/l). However, the males and the Caucasian
females had lower mean values, 1.555 \pm 0.024 kg/l (\(P =
0.031\)) and 1.562 \pm 0.022 kg/l (\(P = 0.042\)), respectively, and
a higher mean D\(_{\text{RES}}\) was observed in the female African-
American subjects, 1.578 \pm 0.019 kg/l (\(P < 0.001\)) compared
with Siri’s (23) value of 1.565 kg/l.

The relationships between D\(_{\text{RES}}\) and age and weight are
presented for males (age: \(r = -0.09\), \(P = 0.629\); weight: \(r =
0.38\), \(P = 0.040\)) and females (Caucasian, age: \(r = -0.42\), \(P <
0.001\); weight: \(r = 0.12\), \(P = 0.073\); African-American, age:
\(r = -0.11\), \(P = 0.345\); weight: \(r = 0.30\), \(P = 0.007\)) in Fig.
2. Thus there were significant simple linear correlations be-
tween D\(_{\text{RES}}\) and weight in males, between D\(_{\text{RES}}\) and age in
Caucasian females, and between D\(_{\text{RES}}\) and weight in African-
American females.

Multiple regression analysis models for D\(_{\text{RES}}\) are presented
in Table 3. Sex, age, weight, race, and two-way interactions of
these variables were examined as potential covariates in the
model with all subjects combined. There was a significant
sex \(\times\) age interaction (\(P < 0.001\)), leading us to carry out the
remaining analyses in men and women separately. For males,
there were no race \(\times\) age (\(P = 0.292\)) or race \(\times\) weight
interactions (\(P = 0.072\)). In contrast, the race \(\times\) age interaction
in females was significant (\(P = 0.004\)), leading us to develop
sex and race-specific regression models.

The model predicting D\(_{\text{RES}}\) in males had only weight as a
significant predictor variable (\(P = 0.040\)). In Caucasian fe-
males, age and weight were significant residual mass predictor
variables (age: \(P < 0.001\); weight: \(P = 0.021\)). For the
African-American females, only weight was a significant pre-
dictor variable in the model (\(P = 0.007\)).

Application to Independent Sample

TBW and BV were used to calculate FM with our adjusted
3C model coefficients and Siri’s 3C model coefficients (23).
The results are expressed as percent (% FM).

The %FM difference was correlated with weight in males,
African-American females, and Caucasian females and with

![Fig. 2. Density of residual mass (D\(_{\text{RES}}\)) vs. independent vari-
ables of age (y) and weight (kg) for males, Caucasian females
(○), and African-American females (∆).](image-url)
age for Caucasian females (all \( P < 0.001 \), Fig. 3). There were no differences between the two \%FM estimates for males at a weight of \( \sim 80 \) kg, however. Siri’s model overestimated \%FM by 0.5% and underestimated \%FM by 0.5% at weights of \( \sim 60 \) and 100 kg, respectively.

Siri’s formula underestimated \%FM in the African-American females by \( \sim 0.5\% \) at a weight of 60 kg and by 1% at 100 kg. Overall, for Caucasian females the weight effect was quite small (<0.5% over a 50-kg range) and significant only after adjusting for age in our multiple regression analysis model. The age effect was larger, with Siri’s model and our new model providing similar results at 30 yr but with Siri’s model then overestimating \%FM by up to \( \sim 1\% \) by 90 yr.

**DISCUSSION**

The classical 3C model suggested by Siri in 1961 now fills an important gap in metabolism research. No other approach is presently capable of providing reliable fat and FFM estimates in patients with severe obesity. This renewed importance of the 3C model led us in the current study to critically evaluate fundamental model assumptions.

Siri developed his 3C model on the basis of the limited data available at the time (22, 23). We made minor revisions to his formula, as noted earlier (i.e., Eq. 14), for the density of fat and water values adjusted for average body temperature (36°C) rather than core temperature (37°C). Siri assumed residual mass consisted of two components, \( M \) and \( \text{TBPro} \), that are present in the ratio \( M/\text{TBPro} \) of 0.35. This assumption of stable proportionality of \( M \) and \( \text{TBPro} \) then allowed calculation of \( D_{\text{RES}} \), an assumed constant in the 3C model. At the time of model development, Siri had values only for bone ash and \( \text{TBPro} \) on five cadavers, four males and one female. He applied this data with a rough estimate of mineral density (3 kg/l) to derive values for \( \alpha \) and \( D_{\text{RES}} \). No corrections were made to convert the cadaver bone mineral ash to total mineral or to consider the separate

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**Table 3. Models for predicting residual mass density**

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Goodness of Fit</th>
<th>Intercept ( \text{kg/l} )</th>
<th>Adjusted ( R^2 )</th>
<th>SEE, kg/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>0.001 (0.0004)*§</td>
<td>1.486 (0.032)*†</td>
<td>0.111</td>
<td>0.023</td>
</tr>
<tr>
<td>C females</td>
<td>-0.001 (0.0001)*+</td>
<td>1.583 (0.010)*†</td>
<td>0.190</td>
<td>0.020</td>
</tr>
<tr>
<td>AA females</td>
<td>0.001 (0.0002)*+</td>
<td>1.541 (0.014)*†</td>
<td>0.190</td>
<td>0.020</td>
</tr>
</tbody>
</table>

*Estimate of regression coefficient; SEE (standard error of estimate) in parentheses. † \( P < 0.001 \), ‡ \( P = 0.01 \), § \( P < 0.05 \).
convenience sample. DRES tends to be lower in men (1.555 ± 0.022 kg/l) compared with African-American (1.578 ± 0.019 kg/l) females. Thus the specific features of our study sample, particularly the much larger number of women, ultimately determined the observed “average” DRES of 1.565. The DRES prediction models (Table 3) or these average DRES values (Table 1) could be used to develop more specific 3C fat mass estimation formulas for each of the respective groups.

When the developed sex- and race-specific DRES formulas were applied to estimate the “errors” arising with application of Siri’s 3C model, in general we observed deviations of less than ~2% from those predicted from our “corrected” models. The magnitude of these error estimates can be viewed by taking an extreme example, elderly normal-weight Caucasian women compared with obese African-American women. The %FM estimate in elderly Caucasian women would be high by ~1% and in the African-American women low by ~1%, a difference of ~2%. Although these are not relatively large errors in estimating relative fatness, the biases might become important when questions such as subtle race differences in resting energy expenditure are examined (21).

A related question, one that prompted the current study, is the %FM estimation errors arising when Siri’s 3C model is applied in persons with severe obesity. To estimate these errors, we must extrapolate DRES estimates beyond those of the maximum model development group weight of ~100 kg. This is a reasonable extension, as no curvilinear components were observed in our developed DRES prediction model in the present study cohort. We can estimate the expected error in %FM for males and African-American females by a simple extension of the regression lines presented in Fig. 3, which illustrates the differences between the original and corrected models when applied to an independent sample of subjects. Siri’s model would underestimate %FM by 1.5 to 2.0% in males and African-American females when weights are in the severely obese range of 150–200 kg. As noted earlier, these are not extremely large errors, but their significance must be judged in the context of the measurement application.

Study Limitations

The current study applied state-of-the-art methods that allowed the first derivation of residual mass density in vivo. Nevertheless, there are some limitations of the present investigation. Our convenience sample did not have an adequate size, racial diversity, and weight variation to accommodate all of the issues surrounding 3C model development, although our findings do reveal potential sources of model error. Our analyses were based on a cross-sectional sample, and the extent to which subjects changing weight over time conform to the model predictions is unknown. We anticipate that our revised 3C model may find application to the study of body composition changes, for example, in subjects undergoing bariatric surgery, but such studies should be viewed with caution pending validation of the revised models on longitudinal data.

Conclusions

In the current study, we critically examined the classic Siri 3C model in living subjects. We corrected Siri’s model on the basis of average body temperature values and established that, in general, this model is appropriate for use in adult women and men who range widely in race, age, and weight. More specific 3C models were also developed for use in males, females, Caucasian females, and African-American females. These subject-specific models may reduce body composition measurement bias when studies are aimed at detecting small between-group differences at the extremes of body size. These observations provide critical insights and practical opportunities for continued use of the 3C model in selected populations.

GRANTS

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REFERENCES


