Estimation of total-body and limb muscle mass in hemodialysis patients by using multifrequency bioimpedance spectroscopy\textsuperscript{1–3}

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ABSTRACT

Background: Skeletal muscle mass can be measured noninvasively with magnetic resonance imaging (MRI), but this is time-consuming and expensive.

Objective: We evaluated the use of multifrequency bioimpedance spectroscopy (BIS) measurements of intracellular volume (ICV) to model total-body skeletal muscle mass (TBMM) and limb skeletal muscle mass in hemodialysis patients.

Design: TBMM was measured by MRI in 20 male and 18 female hemodialysis patients with a median (range) age of 54 y (33–73 y), weight of 78.9 kg (43.2–120 kg), and body mass index (BMI; in kg/m\(^2\)) of 27.3 (19.4–46.6). We measured total body water (TBW) by using D\(_2\)O dilution, extracellular volume (ECV) as bromide space, and ICV as TBW minus bromide space. Total body potassium (TBK) measured as 4\(^{0}\)K was used as an independent model of TBMM. BIS was used to measure whole-body TBW (ankle to wrist) and TBW in the arms and legs. BIS-estimated ICV was used to construct models to calculate limb muscle mass and TBMM. The latter was compared with models derived from isotopic methods.

Results: BIS yielded a model for TBMM [TBMM = 9.52 + 0.331 × ICV + 2.77 (male) + 0.180 × weight (kg) − 0.133 × age] (\(R^2 = 0.937, P < 0.0001\)) as precise as TBK-measured TBMM [TBMM = 1.29 + 0.00453 × TBK (mEq) + 1.46 (male) + 0.144 × weight (kg) − 0.0565 × age] (\(R^2 = 0.930, P < 0.0001\)) or isotopic methods. BIS models were also developed for measuring leg and arm muscle mass.

Conclusion: BIS provides an estimate of TBMM that correlates well with isotopic methods in approximating values obtained by MRI and extracellular fluid, total body water, bioimpedance spectroscopy, and TBW in the arms and legs. BIS-estimated ICV was used to construct models to calculate limb muscle mass and TBMM. The latter was compared with models derived from isotopic methods.

INTRODUCTION

The evaluation of nutritional status in dialysis patients is both important and quantitatively difficult. Changes in body composition consistent with malnutrition are frequent in long-term hemodialysis patients and are powerful predictors of mortality (1, 2). Anthropometric measurements of nutritional status frequently are operator dependent. Formulas using those measurements to calculate total body water (TBW) are imprecise and in poor agreement with direct measurements provided by isotope dilution, especially in the obese and in dialysis patients. Body mass index (BMI) is associated with a low relative risk of mortality in hemodialysis patients (3). Body composition may differ in patients having the same BMI. Creatinine can be used to model the relative effects of fat and muscle mass (3), but the availability of an independent method of assessing muscle mass could have value in distinguishing the contributions of muscle and fat to morbidity associated with different BMIs.

Magnetic resonance imaging (MRI) provides a precise measure of the volume of fat, muscle, and bone compartments, depending on the number of slices (4). Volumes are then transformed to masses. Muscle mass is 1.04 times muscle volume (5, 6).

We designed this study to establish whether regression models could be developed to estimate whole-body muscle mass as well as limb skeletal muscle mass in hemodialysis patients by using bioimpedance spectroscopy (BIS) and whether the results obtained were not significantly different from those obtained by using other standard and accepted techniques. Measurement of the quantity of potassium in the TBK also defines the intracellular volume (ICV) (7). The clinical use of measurement of TBK is limited, however, by the availability of instrumentation. Isotopic methods also provide precise evaluations of intracellular and extracellular compartments. Estimation of TBW by using the dilution of isotopically labeled water (D\(_2\)O) combined with evaluation of extracellular space by using bromide allows the calculation of ICV by subtraction.

Because of its availability and simplicity, bioelectrical impedance analysis (BIA) has significant potential as a complement to standard anthropometric techniques for assessing the nutritional status of dialysis patients (8). Whereas single-frequency BIA

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provides data that are useful for predicting mortality in populations (9, 10), the output data (phase angle and reactance) are not readily comparable to other methods that provide estimates of physiologically recognizable compartments, such as ICV, extracellular volume (ECV), and fat-free mass (8). Furthermore, BIA relies on a single frequency, 50 kHz (11).

Isotopic methods are restricted to measurement of whole-body fluid volumes. In contrast, both MRI and BIS (depending on electrode placement) can measure regional tissue compartments or fluid distribution. Thus, we also sought to ascertain whether limb muscle mass as measured by MRI could be modeled by measurements of ICV in the arms and legs.

SUBJECTS AND METHODS

Subjects

Forty-two hemodialysis patients (19 F, 23 M) aged >18 y were chosen so as to encompass a wide range of BMIs and ages. All subjects had been on maintenance hemodialysis for ≥3 mo before the study.

All subjects provided written informed consent to their participation. The institutional review boards of St Luke’s, Beth Israel, and the University of California, Davis, hospitals approved the study protocol.

Methods

On the day of a regularly scheduled hemodialysis session, the subjects were studied 3 h before initiation of the dialysis treatment. The study began with the administration of D2O and sodium bromide, as described below. After the administration of these isotopes, the subject was then placed in the 4-pi counter. On exiting the counter, the patient was placed in a recumbent position as described below for measurement of bioimpedance. After this measurement, the patient underwent an MRI scan to measure muscle mass. The patient was then transported to the dialysis unit, where blood was obtained before the initiation of dialysis to include defined segmental BIS in the leg and wrist and shoulder) and leg (between electrodes at great trochanter and ankle). A switch was used to transfer data accumulation from the whole body and segments to the Xitron device (4, 12). Raw data derived from these measurements included resistance, reactance, phase angle, and impedance. A program provided by Xitron based on the Cole-Cole model was used to calculate segmental and wrist-to-ankle extracellular and intracellular resistance (R_E and R_I, respectively (14)). Calculations of wrist-to-ankle ECV and ICV were based on the variables R_E, R_I, and body weight and included constants for resistivity, body geometry, and body density (14). Previously published equations (14, 15) were used to calculate ECV and ICV (see below). TBW was calculated as the sum of ECV and ICV by using the whole-body measurements alone.

Patients were then transported to the hemodialysis unit and again weighed at 3 h after the initial dose of D2O and bromide; blood for measurement of both D2O and bromide was obtained before dialysis. At that time, immediately before the initiation of dialysis, an additional 5 mL blood was drawn for measurement of both D2O and bromide so that their respective volumes of distribution could be determined by isotope dilution (16). The dose concentration in the collected specimen is measured on a single-frequency infrared spectrophotometer after the specimen is lyophilized. The TBW volume is calculated by dividing the dose by the net D2O concentration in specimen. The precision for the TBW measurement by this method is ±1.5%. Measurements of bromide concentration are carried out on an HPLC system (16).

The CV of measurement of bromide dilution is 1.4%.

Methods

ECV = \frac{K_{ECV} \cdot (H^2 \cdot W / R_b)^{2/3}}{1 + \left( \frac{ICV}{ECV} \right)^{2/3}} (1)

where H is body height in cm, W is body mass in kg, and R_b is given in Ω. \( K_{ECV} \) is a factor related to body geometry, density, and resistivity, according to the following equation (14):

\[ K_{ECV} = \frac{1}{1000} \left( \frac{D_b^2 \cdot \rho_{ECV}}{\rho_{ECV} \cdot D_b} \right)^{1/3} (2) \]

where \( \rho_{ECV} \) is the resistivity of extracellular fluid, \( D_b \) is body density considered as a constant value (kg/L), and \( \rho_{ECV} \) is a coefficient of body height related to geometric limb size (14). \( K_{ECV} \) is considered a constant on the basis of the assumption that there are relatively uniform proportions between limbs and total body height (14). Intracellular fluid volume was calculated by using the following equation (14):

\[ 1 + \left( \frac{ICV}{ECV} \right)^{2/3} = \left( R_E + R_I / R_b \right) \times \left( 1 + K_{ICV} \cdot ICV / ECV \right) (3) \]

where \( \rho_{ECV} \) is the resistivity of intracellular fluid, \( k_p \) is the ratio of intracellular to extracellular fluid resistivity (kg/L), and \( R_b \) is given in Ω. \( \rho_{ECV} \) was 273.9 Ω cm for males and 264.9 Ω cm for females, whereas \( \rho_{ICV} \) was 40.5 Ω cm for males and 30 Ω cm for females.

Segmental ECV and ICV were calculated for the arms and legs by using the following equations:

\[ ECV_i = \frac{2}{1000} \left( \rho_{ECV} \times L_i^3 / R_b \right) (4) \]

and

\[ ICV_i = \frac{2}{1000} \left( \rho_{ICV} \times L_i^3 / R_b \right) (5) \]
where \( \rho \) represents factors for extracellular (\( \rho_e = 47 \text{ \Omega cm} \)) and intracellular (\( \rho_i = 273.9 \text{ \Omega cm} \)) resistivity, \( L_i \) represents segmental length, \( \rho_{ex} \) represents segmental extracellular resistance, and \( R_i \) represents segmental intracellular resistence (the subscript \( i \) represents the arm or leg) (15).

Segmental ECV and ICV of the arms and legs were derived by applying the respective parts of equations 4 and 5 separately.

Establishing error in BIS measurement of ICV in hemodialysis patients

When performed 3 times a week, hemodialysis is generally conducted after either a 1- or 2-d interval. It is possible, therefore, that fluid volumes may be affected by the span of time between dialysis treatments, during which an artifact may be introduced. To establish the precision of ICV measurement with BIS in dialysis patients and to ascertain whether ICV measurements were sensitive to the time elapsed between treatment, we measured ICV repeatedly in 13 hemodialysis patients. Measurements were all conducted within the 2 h before initiation of hemodialysis but either 1 or 2 d after the previous treatment. Four of the patients were women.

Statistical analysis

Models were created by using a forward stepwise multiple regression model (JMP software, version 5.0.1; SAS Inc, Cary, NC). The dependent variable was muscle mass measured by MRI. Models were created by using age; sex; BMI; height; body surface area; diabetic status; and either TBW measured with \( \text{D}_2\text{O} \) dilution, ECV measured by using bromide dilution, or ICV measured by using the difference between these variables (isotopic method), TBK, and BIS estimates of compartmental fluid volumes. In the latter instance, BIS estimates of TBW, ICC, and ECV were initially all entered as independent variables. Recognizing that ECV, unlike ICV, may vary in dialysis patients independently of body cell mass because of fluid retention between dialysis treatments, a BIS model was forced with the use of ICV only and compared with the best-fit model using all fluid compartments.

To estimate the independent contribution of BIS measurements in the absence of sex, weight, age, BMI, and height, BIS estimates of ICV only were added, and other variables were deliberately omitted. MRI measurement of muscle volume was multiplied by 1.04 to calculate muscle mass in kilograms (5, 6). Variables that did not contribute significantly to the regression model were not included in the final regression output.

RESULTS

Complete measurements were available in 38 of the subjects (20 men, 18 women) (Table 1). The patients were from the multiethnic area of Upper Harlem in New York City: 33 patients were African American, 3 were Hispanic, and 2 were Asian. Twelve of the patients were diabetic.

Several models were fitted with the MRI measurement of muscle volume by using either isotopically derived data (\( \text{D}_2\text{O} \) and bromide), TBK data, or data derived from anthropometric measures and BIS (Table 2). Total mean (±SD) skeletal muscle as measured by MRI was 24.0 ± 1.1 kg (range: 12.6–38.4 kg) (Table 1). Muscle represented 30.6% of body weight (range: 20.9 –41.8%). TBW measurements obtained by using \( \text{D}_2\text{O} \) dilution (Table 1) and by using BIS were significantly correlated. \( R^2 = 0.785, P < 0.0001 \). No bias was evident by Bland-Altman analysis.

ECV measurements calculated from the bromide volume of distribution and from whole-body BIS also were not significantly correlated.

\[ R^2 = 0.785, P < 0.0001 \]

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (10th percentile)</th>
<th>90th percentile</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>53.5 (40.8)</td>
<td>69</td>
<td>33–73</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.695 (1.53)</td>
<td>1.80</td>
<td>1.49–1.85</td>
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<tr>
<td>Weight (kg)</td>
<td>78.9 (57.6)</td>
<td>102</td>
<td>43.2–120</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.5 (23.1)</td>
<td>37.2</td>
<td>19.4–46.6</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.90 (1.55)</td>
<td>2.16</td>
<td>1.34–2.35</td>
</tr>
<tr>
<td>TBK (mEq)</td>
<td>3282 (2322)</td>
<td>4191</td>
<td>2020–4345</td>
</tr>
<tr>
<td>TBW (L)</td>
<td>40.6 (29.4)</td>
<td>49.7</td>
<td>28.3–54.2</td>
</tr>
<tr>
<td>TBW (L)</td>
<td>41.4 (25.4)</td>
<td>52.1</td>
<td>22.3–57.7</td>
</tr>
<tr>
<td>ECV (L)</td>
<td>19.0 (10.6)</td>
<td>23.7</td>
<td>6.7–28.6</td>
</tr>
<tr>
<td>ECV (L)</td>
<td>19.2 (13.4)</td>
<td>23.2</td>
<td>11.2–26.8</td>
</tr>
<tr>
<td>ICV (L)</td>
<td>21.6 (14.7)</td>
<td>27.5</td>
<td>13.3–28.6</td>
</tr>
<tr>
<td>ICV (L)</td>
<td>22.8 (15.7)</td>
<td>29.4</td>
<td>14.6–33.9</td>
</tr>
<tr>
<td>ICV (L)</td>
<td>22.0 (12.7)</td>
<td>28.8</td>
<td>10.5–31.7</td>
</tr>
<tr>
<td>TBMM (kg)</td>
<td>24.1 (15.4)</td>
<td>33.0</td>
<td>12.6–38.4</td>
</tr>
<tr>
<td>Arm muscle mass (kg)</td>
<td>3.85 (2.18)</td>
<td>5.22</td>
<td>2.08–5.72</td>
</tr>
<tr>
<td>Leg muscle mass (kg)</td>
<td>11.3 (7.7)</td>
<td>16.0</td>
<td>6.1–16.1</td>
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Table 2

<table>
<thead>
<tr>
<th>Model for TBMM</th>
<th>BIS</th>
<th>TBK²</th>
<th>Isotope</th>
</tr>
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<tr>
<td>Constant</td>
<td>9.52</td>
<td>1.29</td>
<td>10.5</td>
</tr>
<tr>
<td>IVC coefficient¹</td>
<td>0.331</td>
<td>0.00453</td>
<td>0.101</td>
</tr>
<tr>
<td>Male sex</td>
<td>2.77</td>
<td>1.46</td>
<td>3.32</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.180</td>
<td>0.144</td>
<td>-0.0565</td>
</tr>
<tr>
<td>Age (y)</td>
<td>-0.113</td>
<td>-0.0565</td>
<td>-0.113</td>
</tr>
<tr>
<td>SEE (kg)</td>
<td>1.85</td>
<td>1.84</td>
<td>2.00</td>
</tr>
<tr>
<td>( R^2 )</td>
<td>0.937</td>
<td>0.930</td>
<td>0.916</td>
</tr>
<tr>
<td>( P )</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

¹ \( n = 38 \), BIS, bioimpedance spectroscopy; TBK, total body potassium; ICV, intracellular volume; TBMM, total-body muscle mass.

² Measured with deuterium oxide dilution.
³ Measured with bioimpedance spectroscopy.
⁴ Measured with sodium bromide dilution.
⁵ Measured with potassium dilution.
⁶ Measured with deuterium oxide minus sodium bromide.
⁷ Measured with magnetic resonance imaging.

Values are mL, except TBK, which is mEq.
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TOTAL-BODY AND LIMB MUSCLE MASS MEASURED WITH BIS

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FIGURE 1. Correlation between total-body muscle mass (TBMM) measured by magnetic resonance imaging (MRI) and a regression model developed by using ankle-to-wrist multifrequency bioimpedance spectroscopy (BIS), age, sex, and weight (whole-body BIS model). The equation used was

\[
\text{TBMM} = 9.52 + 0.331 \times \text{BIS-derived ICV} + 2.77 \times \text{age} + 0.180 \times \text{weight} - 0.113 \times \text{age} \times \text{weight}.
\]

The results of this equation give a value of

\[
\text{SE} = 1.85 \, \text{kg} \left( R^2 = 0.937, P < 0.0001 \right).
\]

The dependent variable was TBMM measured by using MRI. ICV, intracellular volume.

Different, and they correlated with one another (Table 1) \((P < 0.0001, R^2 = 0.501)\). No bias was evident. ICV calculated on the basis of TBK did not differ significantly from that measured with whole-body BIS. Whole-body BIS-measured ICV was \((\bar{x} \pm \text{SEM}) 22.0 \pm 0.92 \, \text{L}\), and that calculated from TBK was \(20.9 \pm 0.72 \, \text{L}\) \((P = 0.532)\). The correlation between the 2 values was 0.889 \((P < 0.0001)\).

TBW in dialysis patients may vary independently of intracellular water because of failed renal function and the resulting expansion of ECV. Furthermore, ECV, even in a given dialysis patient, will vary according to the time since the previous dialysis treatment. Accordingly, we based our BIS model on measurements of ICV alone. With the use of this measure, the best-fit multiple regression model included sex, weight, and age (Table 2 and Figure 1). The coefficients of the regression models are presented in tabular form. Median TBMM estimated by the BIS model was 27.2 kg \((\bar{x} \pm \text{SEM}) 26.0 \pm 1.0 \, \text{kg}; \text{range: } 15.4–35.9 \, \text{kg}\).

Bland-Altman analysis found bias \((R^2 = 0.259, P < 0.001)\) (Figure 2). Median TBMM estimated by the TBK model was 25.5 kg \((\bar{x} \pm \text{SEM}) 24.3 \pm 1.02 \, \text{kg}; \text{range: } 14.9–33.6 \, \text{kg}\).

Bromide space (ECV) was eliminated from the regression model when the \(D_2O\)-measured volume of distribution was included. Much as was seen with BIS analysis, when TBW (volume of distribution of \(D_2O\)) was intentionally omitted from the regression model, ICV calculated as the difference between \(D_2O\) and bromide distribution volume (ICV bromide) provided a model that did not differ significantly from that achieved by the other methods (Table 2). Median TBMM estimated by the isotope dilution model using ICV was 26.7 kg \((\bar{x} \pm \text{SEM}) 25.5 \pm 0.9 \, \text{kg}; \text{range: } 17.3–35.2 \, \text{kg}\).

The correlation between TBMM measured with MRI and measured by using the BIS model described above did not differ significantly from that obtained by using TBK plus the same demographic variables (ie, weight, sex, and age) or from that obtained with the model that used isotope dilution plus age, sex, and weight (Table 2). Thus, ICV measured either with BIS or with isotope dilution provided a model that closely correlated with TBMM measured with MRI. In patients studied to establish the precision of BIS measurements and the variability introduced by time since the previous dialysis treatment, weight was 77.7 ± 15.9 kg \((\text{range: } 56.2–102.4 \, \text{kg}\), BMI 27.0 ± 0.9 \((\text{range: } 19.4–46.6)\), and ICV was 18.5 ± 5.0 L \((\text{range: } 10.8–26.7 \, \text{L}\). ICV was measured 3 times in each patient. The CV of the measurement of ICV was 3.78%. ICV was independent of the length of time after the previous dialysis. ICV measured 1 d after a dialysis treatment was 18.6 ± 1.54 \, \text{L}, and that measured 2 d after treatment was 18.5 ± 1.61 \, \text{L} \((P = 0.599, \text{paired } t \text{ test})\).

Understanding that sex, weight, and age and could predict TBMM without additional information on TBW or ICV, we modeled TBMM versus TBK (mEq), isotope dilution methods, and the measurement of ICV by using BIS alone to establish the specific precision of each volume measurement and by including BIS in the absence of other information, as shown in the following equation:

\[
\text{TBMM(kg)} = 2.074 + 1.064 \times \text{BIS-derived ICV(L)}
\]

where ICV is measured with whole-body BIS \((\text{SE} = 3.28 \, \text{kg}; R^2 = 0.783, P < 0.001)\) (Figure 3).

Bland-Altman analysis using only BIS-derived data for estimation of muscle mass showed no significant bias \((R^2 = 0.0365)\). Thus, regression models that correlate with TBMM measured with MRI can be obtained by using TBK, isotope dilution, and whole-body BIS measurements. However, it may be possible to use segmental measures of fluid compartments with BIS—but not with either TBK or isotope dilution—to estimate arm or leg muscle mass. To test this hypothesis, we developed models relating BIS fluid compartment measurements of the arms and legs to MRI measurements of skeletal muscle mass in these extremities.

To avoid possible variability in the ECV compartment in dialysis patients, the final models for the arms and legs were calculated with the use of BIS measurement of ICV. Total leg muscle mass measured with MRI could be modeled with the use of sex,
age, weight, and segmental ICV by using an ankle-to-hip electrode (Table 3, Figure 4).

Median leg muscle mass as measured with MRI was 11.3 kg (range: 6.1–16.1 kg) (Table 1), and total leg muscle mass as measured by using the BIS model was 12.3 kg ($\bar{x} \pm$ SEM: 13.0 ± 0.5 kg; range: 7.5–18.5 kg). Bland-Altman analysis showed some degree of bias ($R^2$ for the regression = 0.178, $P = 0.01$) (Figure 5). When demographic and anthropometric data were not used, BIS modeling of the leg yielded a strong correlation, but bias was significantly reduced, as seen in Figure 6 and in the following equation:

$$\text{MRI leg muscle mass (kg)} = 4.44 + 1.21 \times \text{ICV (L)} \quad (7)$$

where the relation was $\text{SE} = 2.03 \text{kg} \ (R^2 = 0.63, \text{and} \ P < 0.001)$.

TABLE 3
Models for estimation of segmental muscle mass measured by intracellular volume (ICV) as measured by bioimpedance spectroscopy$^1$

<table>
<thead>
<tr>
<th>Compartment measured</th>
<th>Leg</th>
<th>Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>4.53</td>
<td>1.69</td>
</tr>
<tr>
<td>ICV coefficient (L)</td>
<td>0.5005</td>
<td>0.301</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.535</td>
<td>0.603</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.0839</td>
<td>0.0234</td>
</tr>
<tr>
<td>Age (y)</td>
<td>-0.0483</td>
<td>-0.123</td>
</tr>
<tr>
<td>SEE (kg)</td>
<td>1.16</td>
<td>0.306</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.890</td>
<td>0.933</td>
</tr>
<tr>
<td>$P$</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

$^1 n = 38$. The dependent variable was muscle mass measured by magnetic resonance imaging. Best-fit multiple regression models were used for the correlation between total limb muscle mass measured by magnetic resonance imaging and modeled by using sex, weight, age, and ICV measured by bioimpedance spectroscopy. Equations are formulated as $\text{TBMM} = \text{Constant} + a \times \text{ICV} + b \times \text{sex} + c \times \text{weight} + d \times \text{age}$, where $a$ is the ICV coefficient, $b$ is sex, $c$ is weight, and $d$ is age.

Bland-Altman analysis showed no significant bias and an intercept of nearly zero ($R^2 = 0.088, P = 0.073$). Analysis of arm composition gave comparable results (Table 3). Total arm muscle mass measured by using MRI was 3.9 kg (range: 2.1–5.7 kg), and that measured by using the BIS model was 4.3 kg ($\bar{x} \pm$ SEM: 4.00 ± 0.14 kg; range: 2.7–5.6 kg), as shown in Figure 7 and the following equation:

$$\text{MRI arm muscle mass (kg)} = 1.69 + 0.301 \times \text{ICV(L)} + 0.603 \text{male} + 0.0234 \times \text{weight (kg)} - 0.123 \times \text{age (y)} \quad (8)$$

where the relation was $\text{SE} = 0.306 \text{kg} \ (R^2 = 0.933, P < 0.0001)$. 

FIGURE 3. Correlation between total-body muscle mass (TBMM) measured by magnetic resonance imaging (MRI) and a regression model developed by using ankle-to-wrist multifrequency bioimpedance spectroscopy (BIS) measurement of intracellular volume (ICV) alone with no demographic variables. The equation used was TBMM (kg) = 2.074 + 1.064 × BIS-derived ICV (L). The results of this equation give a value of SE = 3.28 kg ($R^2 = 0.78, P < 0.001$). Bland-Altman analysis found no bias [SD = 0.94 ± 3.11 kg ($R^2 = 0.0365, P = 0.15$); data not shown]. The dependent variable was skeletal muscle mass measured by using MRI.

FIGURE 4. Correlation between leg muscle mass measured by magnetic resonance imaging (MRI) and a regression model developed by using ankle-to-limb multifrequency bioimpedance spectroscopy (BIS), age, sex, and weight. The equation used was MRI leg skeletal muscle (kg) = 4.53 + 0.5005 × ICV (L) + 1.535 (male) + 0.0839 × weight (kg) − 0.0483 × age (y). The results of this equation give a value of SE = 1.16 kg ($R^2 = 0.890, P < 0.001$). The dependent variable was leg skeletal muscle mass measured by MRI, ICV, intracellular volume.

FIGURE 5. Bland-Altman plot of the difference between magnetic resonance imaging (MRI) and bioimpedance spectroscopy (BIS) estimates of leg skeletal muscle mass model versus the average value for leg skeletal muscle mass computed by the intracellular volume (ICV) model and leg muscle mass measured by MRI [${\bar{x} \pm SD}$ estimate: $-0.98 \pm 1.16$ kg ($R^2 = 0.178, P = 0.01$)].
Bland-Altman analysis showed significant bias ($R^2 = 0.448$, $P < 0.001$) (Figure 8). As we observed with the leg, when demographic and anthropometric variables were removed from the relation, a model that correlated total arm muscle estimated by BIS with MRI measurement of muscle mass was established, as shown in Figure 9 and the following equation:

$$\text{MRI arm muscle mass (kg)} = -0.774 + 1.1 \times \text{ICV (L)}$$  \hspace{1cm} (9)

where the relation was $SE = 0.63$ kg ($R^2 = 0.69$, $P < 0.001$), but, in this instance, the relation was without significant bias ($R^2 = 0.0636$, $P = 0.128$).

**DISCUSSION**

Skeletal muscle mass represents a large fraction of ICV. Thus, it is possible to construct models using isotopic or bioelectrical measures of ICV that model MRI measures of muscle mass. Because of the nature of isotopic measurements, limb ICV cannot be measured easily or at all. In contrast, BIS lends itself to measurements of both whole-body fluid volumes and volumes of defined anatomic compartments—in this case, limb ICV. This study shows that, in a cohort of mostly African American hemodialysis patients, multifrequency BIS can be used to estimate TBMM in addition to muscle mass of both the arms and legs.

Because potassium is largely an intracellular cation, skeletal muscle mass can be estimated by measuring TBK in healthy adults (17). Dialysis patients may accumulate potassium, and thus one may question the validity of TBK in predicting muscle mass in these patients. Because $>95\%$ TBK is intracellular at a concentration $\approx 40$ times that in the extracellular compartment, the modest increase in extracellular potassium that might be encountered in dialysis patients should have little effect on the...
use of this measure (18). A second potential problem that might confound results in patients with chronic kidney disease is that of alteration of intracellular electrolyte composition. Cotton et al (19) reported that patients with creatinine clearances < 6.3 mL/min had low resting transmembrane potential differences and low intracellular potassium. However, hemodialysis 3 times/wk was sufficient to restore intracellular potassium to a concentration that did not differ significantly from that in normal subjects (155 ± 4.9 and 155 ± 4.3 mEq/L, respectively).

Empirical models that rely on measures of TBW have been developed to describe total protein mass (20). Hemodialysis patients, however, accrue extracellular fluid between dialysis treatments. Although we were able to construct a model of precision whose results did not differ significantly between the use of isotope dilution and BIS measures of TBW, it is possible that the variability of ECV in dialysis patients may make such models vary as functions of the time since the previous dialysis treatment. Models of TBMM developed by using BIS measures of ICV had regression coefficients that did not differ significantly from those obtained by using TBK or isotope dilution estimates of ECV. Similarly, measurement of ICV in either the arms or legs provided models that correlated well with measured limb muscle mass.

We have developed regression models by using multifrequency BIS with regression coefficients similar to those obtained by using isotopic techniques when they were compared with independently measured values for muscle mass. In addition, we have established that segmental measurements of limb muscle mass provided by multifrequency BIS estimates of ICV correlate closely with MRI measures of limb muscle mass. Bias in the relations is introduced by including various demographic or anthropometric measures in the regression model, not by using the BIS measures of volume. Estimates of limb muscle mass obtained by using BIS volume measurements are without notable bias. Whereas isotopic methods are not capable of analyzing compartmental muscle masses, BIS is of sufficient quality to provide this information. This information could allow for quantitative structural evaluation of rehabilitation efforts after injury to associated joints. Furthermore, we have established that ICV does not vary significantly with intradialytic periods, which would be of clinical interest.

Whereas BMI and adiposity have been found to be associated with low mortality among dialysis patients, indexes associated with lean body mass, such as volume of distribution of urea, independently predict survival (21, 22). Similarly, TBK, a measure of ICV, positively predicts survival in chronic disease (23–25).

Because visceral volume increases at a lower rate than does muscle mass (26), muscle mass contributes a greater fraction of tissue mass as body cell mass increases (27). This is of some importance, because the resting energy expenditure of skeletal muscle is significantly less than that of organ tissues (28), and, thus, energy needs as a fraction of the body mass would be expected to decline as body cell mass increases (27, 29). Indexes associated with greater muscle mass likewise predict survival among patients with end-stage renal disease (30).

All of the models we developed that use measures of ICW alone implicitly assume that a fixed fraction of body cell mass is composed of muscle within a group of persons with a similar body cell mass. The addition of weight, sex, and age provides more information; however, all measurements other than MRI must be used with the understanding that muscle mass may differ from that obtained by using the model in subjects whose body morphometry differs widely from average values.

Measurement of lean body mass in dialysis patients is confounded by the expansion of extracellular fluid, a component of lean body mass. More precise measures of ICV should provide a better measure of somatic protein stores (body cell mass rather than lean body mass, which includes ECV and bone) than does measurement of lean body mass alone. Anthropometric measures are limited by operator variability and precision (31). BIA has been found to be useful in monitoring the nutritional status of dialysis patients (8). However, the use of BIA in dialysis patients has mostly relied on measurement of phase angle, and those studies have not been extended to segmental analysis (8, 32).

Nutritional status can be evaluated longitudinally by the monitoring of serum albumin. In contrast to the measurement of serum protein, the estimation of intracellular mass presents more of a challenge. Measurement of TBK by using 40K or of total body nitrogen by using neutron activation provides excellent measures of body cell mass (33); however, both procedures are time-consuming, expensive, and not widely available. Evaluation of TBW by isotope dilution of extracellular space using bromide (34, 35), chloride (34), inulin (36), or sulfate (34) also is not easily applicable clinically. MRI also provides a measure of specific extracellular and intracellular compartments (28, 37). Measurement of the quantity of potassium either in the total body or regionally also defines the volume of intracellular water (7).

We have calibrated whole-body BIS with other measures of body composition, specifically 40K, MRI muscle, and isotope dilution techniques of intracellular water and extracellular water that correlates sufficiently well to isotopic measures to be useful in describing body composition. In contrast to isotopic and MRI measurements, BIS measurements are noninvasive and inexpensive, and the procedure is portable. The precision of BIS in estimating ECV and ICV is sufficiently good (published CV: ≈3–6%; 38, 39) to be useful in longitudinal analysis of individual patients by providing the capability of measuring muscle mass regionally or segmentally in longitudinal studies, in rehabilitation after surgery or injury, and after training in the gymnasium.

GAK conceived of and designed the project, designed the protocol, did the regression modeling, and participated in manuscript preparation. FZ supervised the acquisition of the bioimpedance spectroscopy (BIS) data; analyzed the BIS data; developed the concept of regional BIS analysis, including the mathematical model to measure intracellular volume, extracellular volume, and total water in individual body segments; and participated in manuscript preparation. SS recruited patients, and SS and CK performed the BIS measurements. SBH analyzed the magnetic resonance imaging data. JW supervised and performed the total body potassium measurements as well as measurements of both D2O and bromide volumes of distribution. MKK supervised the acquisition of data for the last 20 patients studied and participated in manuscript preparation. NWL participated in the study concept and design and participated in manuscript preparation. None of the authors had any personal or financial conflict of interest.

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