Nutritional Assessment With Bioelectrical Impedance Analysis in Maintenance Hemodialysis Patients

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ABSTRACT
Protein energy malnutrition is common among persons with ESRD and contributes substantially to morbidity and mortality. The usual methods of nutritional assessment, such as anthropometry, can be misleading because of altered tissue hydration. Bioelectrical impedance analysis (BIA) has been recommended by some as a practical nutritional assessment tool but has not been validated in patients with ESRD. Thirty-three stable patients on maintenance hemodialysis were evaluated in an ambulatory clinical research center with simultaneous BIA, dual-energy x-ray absorptiometry, and deuterium oxide (D₂O) and sodium bromide (NaBr) isotope dilution studies. Standard determinations of total body water (TBW) and body cell mass (BCM) were obtained and compared with values estimated by BIA. Two separate outpatient BIA measurements were also obtained approximately 2 wk before and after the clinical research center evaluation. BCM estimated by BIA was directly correlated (r = 0.92, P < 0.0001) with BCM determined by DEXA and NaBr. TBW estimated by BIA was directly correlated (r = 0.96, P < 0.0001) with TBW determined by deuterium oxide dilution. The reactance to resistance ratio (Xc/R) derived from BIA was inversely correlated (r = -0.73, P < 0.0001) with the extracellular water/TBW ratio determined by NaBr/D₂O. Bland-Altman analyses showed that for TBW, BIA was in excellent agreement with D₂O dilution. BCM was modestly underestimated by BIA compared with the dual-energy x-ray absorptiometry/NaBr standard and was adjusted by linear regression. The coefficients of variation on repeated BIA measurements were below 4%, demonstrating test-retest reliability. BIA is a valid and reliable method of nutritional assessment in maintenance hemodialysis patients.

Key Words: Bioelectrical impedance analysis, dual-energy x-ray absorptiometry, body cell mass, coefficient of variation, correlation

Protein energy malnutrition is present in 20 to 40% of persons on maintenance dialysis (1-5) and is an important determinant of morbidity and mortality in ESRD (6-10). Traditional methods of nutritional assessment, such as change in body weight, dietary assessment, and anthropometry, are relatively ineffective at identifying malnutrition in this population, particularly early in its course, because of limited test discrimination and the lack of reliable standards of comparison (2, 11, 12). biochemical surrogates of nutrition, such as serum albumin, creatinine, transferrin, and cholesterol, can be useful in identifying high-risk groups but are often abnormal only late in the course of a deteriorating nutritional state and can be confounded by concomitant liver disease, iron-deficiency anemia, and chronic inflammation (9, 12-15). More sophisticated methods of body composition analysis, such as neutron activation analysis or total body potassium, can be used to quantify body cell mass (BCM) and other body compartments (16-18) but are costly and not widely available. A convenient method that could assist in the diagnosis of malnutrition in the chronic dialysis unit setting early in its course would be desirable, so that various resources, such as dietary counseling, social supports, and enteral or parenteral nutrition therapies, could be efficiently aimed at high-risk patients before malnutrition-related complications develop.

Bioelectrical impedance analysis (BIA) has been proposed as one such method. BIA is based on the bioelectrical principle of impedance (Z), the vector sum of resistance and reactance.
Resistance (R) is the opposition to electrical current related to the length and diameter of a cylinder. The human body resembles a set of serially connected cylinders (e.g., arms, legs, and trunk) with known height and relatively constant diameter. If length and diameter are known, R reflects the volume of the cylinder’s fluid contents, which carry an electrical charge. Reactance (Xc) reflects the portion of impedance due to the presence of capacitive elements, such as cell membranes. Resistance (R) is much larger in magnitude than reactance (Xc) in a series model, but much smaller than Xc in a parallel model. Fat mass (and fat-free or lean body mass) is best predicted with parallel reactance.

Dual-energy x-ray absorptiometry (DEXA) has been used for many years in the diagnosis and ongoing care of patients with osteoporosis and other musculoskeletal disorders, and more recently in body composition analysis (19). DEXA determines the differential attenuation of the body’s tissues to distinct low- and high-energy x-ray beams (70 kVp and 140 kVp), which allows for the quantification of the body’s bone and soft tissue (fat mass and lean body mass) compartments. DEXA can be rapidly performed and entails minimal radiation exposure (less than 5 mrem). However, DEXA rests on an important assumption that may be violated in chronic renal disease, that of uniform tissue hydration, and cannot itself distinguish the relative distribution of intracellular and extracellular water (19). Therefore, concurrent isotope dilution studies are required to calculate BCM, the body compartment most relevant to nutrition and metabolism (20).

The primary purpose of this study was to compare estimates of BCM and total body water (TBW) derived from BIA with those determined by DEXA and isotope dilution studies in a group of ambulatory hemodialysis patients. Secondary study aims were to assess test-retest reliability using BIA and to consider the feasibility of performing BIA in the in-center hemodialysis setting.

METHODS

Study Subjects

Study subjects were nonrandomly selected from four Boston-area dialysis units. Persons aged below 35 or above 75 yr, amputees, and individuals hospitalized within 60 days for a nonvascular access complication were ineligible for the study. Efforts were made to sample a broad cross-section of patients with regard to age, sex, race, primary renal diagnosis, diabetic status, and body habitus. Patients were subjectively rated by two physicians and a registered dietitian as normal, mildly malnourished, or moderately to severely malnourished on a three-point ordinal scale (after Detsky and coworkers [21]) before study results were available. A consensus judgment was reached on all cases. A single 24-h diet recall for energy and protein intake was performed by a registered dietitian. Baseline laboratory tests including a urea reduction ratio obtained within 30 days of the initial BIA evaluation were recorded. Each study participant underwent BIA, DEXA, and deuterium oxide (D2O) and sodium bromide (NaBr) dilution studies performed by the same investigators on a nondialysis weekday at the Brigham and Women’s Hospital Ambulatory Clinical Research Center (CRC). Two outpatient BIA tests were performed by a staff nurse, registered dietitian, or dialysis technician predialysis and postdialysis approximately 1 wk before and after the CRC evaluation. The difference in estimated TBW predialysis and postdialysis was compared with the actual volume of ultrafiltrate determined by change in body weight by calibrated scale. Informed consent was obtained from all patients.

Body Composition/Determination of BCM

Body mass can be grossly divided into two compartments: fat mass and fat-free or lean body mass (LBM). In a multiproportional compartment model (Figure 1), LBM may be partitioned into skeleton and integument, skeletal muscle and visceral organs, and TBW, which is further partitioned into intracellular and extracellular water (ECW). BCM is defined as LBM without bone mineral mass or ECW and is the most metabolically active body compartment (20). For the purpose of this study, the “gold standard” BCM was determined by use of the following equation: Total weight by DEXA - (DEXA bone mineral mass + DEXA fat mass + NaBr ECW). The “gold standard” TBW was determined from the D2O space; the ECW/TBW ratio was determined from the ratio of the NaBr/D2O spaces. Clearly, these standards of comparison are not true gold standards; they too are prone to measurement error (see below). Nevertheless, they are among the most accurate tools available for practical research use and will be referred to herein as “gold standards.”

D2O and NaBr

The D2O was pyrogen free and 99.9% pure (Cambridge Isotope Laboratory, Woburn, MA). A 3% solution of sodium bromide was prepared the day before the CRC evaluation by a research pharmacist using sodium bromide powder (99.6% pure sodium bromide; Spectrum, Gardena, CA) and standard cold sterilization techniques (Millipore GS 0.22-mm-pore size filter; Millipore, Bedford, MA). Venous blood samples were obtained to determine background concentrations of D2O and NaBr. D2O (9 ml) and NaBr (50 ml) were then injected through an intravenous line. Four hours after the injection, venous blood samples were drawn from distinct

Figure 1. Schematic diagram of body composition.
sites to determine the concentrations of D₂O and NaBr at equilibrium. The participants were instructed to refrain from oral intake during the equilibrium period.

Whole blood samples were centrifuged at 3,000 rpm for 15 min. and the plasma was stored in sealed plastic tubes at −20°C until analysis. Concentrations of D₂O were determined by the use of mass spectroscopy (Model 3–60; Nuclide, Bellefonte, PA) (22). The coefficient of variation for the analysis of D₂O by this method is less than 2% and, typically, less than 0.75% (Metabolic Solutions, Merrimack, NH). NaBr concentration was determined by the use of high-performance liquid chromatography (Model 338; Beckman Instruments, Ramon, CA) by a modification of a method previously described (23).

The D₂O space was calculated from the administered dose of the tracer and the concentration at equilibrium, corrected for the background concentration (24). The TBW was derived from the D₂O space by using a correction factor of 1.04 to account for nonaqueous hydrogen exchange (25,26). The ECW was calculated in a manner similar to that for NaBr dilution and corrected for nonextracellular bromide distribution and the Donnan equilibrium (27,28). The TBW and ECW volumes were converted to mass by multiplying by the density of water at 37°C (0.994 g/mL).

DEXA
Subjects were positioned supine and scanned in full-length hospital gowns. TBW, along with component weights of bone mineral, fat tissue, and lean tissue were recorded. Previous validation studies of DEXA have confirmed a high degree of accuracy in these measurements (29). The coefficients of variation at our center for DEXA measurements of bone mineral, fat tissue, and lean tissue were determined to be 0.99, 1.09, and 0.89%, respectively (30). DEXA was performed with the Hologic QDR model 1000 system, and data were calculated with QDR system software version 7.01 (Hologic, Waltham, MA).

BIA
BIA measurements were performed with electrodes placed at the upper and lower extremities in order to determine whole-body impedance. Briefly, an inner electrode was attached to the dorsal surface of the wrist, on the arm without an arteriovenous fistula or graft. An outer electrode was placed on the dorsal surface of the third metacarpal bone. A second pair of electrodes was positioned on the anterior surface of the ipsalateral ankle and the dorsal surface of the third metatarsal bone (31). A low-amplitude, single-frequency, imperceptible current (800 mA at 50 kHz) was introduced via the electrodes on the hand and foot. The voltage drop was detected by the electrodes at the wrist and ankle. The procedure was performed in 5 min or less.

The bioelectrical impedance analyzer used in this study (Model 101; RJL Systems, Clinton Twp, MI) vectored the impedance signal (Z, in ohms, Ω) into resistance (R, Ω) and reactance (Xc, Ω) as a direct series measurement. Resistance (R) and reactance (Xc) were recorded, and the Xc/R ratio was calculated. R and Xc were later mathematically transformed to their equivalent parallel values and adjusted for stature height by the use of exponential relationships to compensate for the irregular geometries of the human body (32). TBW was predicted from impedance (Z). BCM was predicted from parallel reactance.

Statistical Analysis
Correlation was estimated by the use of Pearson product moment coefficients. Linear regression equations were derived by the method of least squares, and 95% prediction and confidence limits were calculated. TBW and BCM by “gold standards” and by BIA were plotted and assessed for agreement by the method of Bland and Altman (33,34). Student’s t tests were used to compare means between methods of measurement. All probability (P) values are two tailed. Statistical analyses were performed with SAS (SAS Institute, Cary, NC).

RESULTS
Study Subjects
Thirty-three subjects completed an evaluation at both CRC and dialysis unit sites. The mean age of study subjects was 55.3 ± 11.8 (mean ± SD) yr. Eighteen subjects (53%) were women; 18 (53%) were of African-American ethnicity. The majority (21; 63%) were judged to be adequately nourished by subjective global assessment. Of the remainder, 11 (32%) were thought to be mildly malnourished; 2 (6%) were felt to be moderately to severely malnourished (one patient with concomitant hepatic failure, one patient with recurrent pancreatitis). Several severely malnourished patients were approached and were either too ill to spend the day in our outpatient CRC or declined our invitation to participate. Diabetic renal disease, hypertensive nephrosclerosis, chronic glomerulonephritis, and polycystic kidney disease were the four most common primary renal diagnoses, accounting for 20 (60%) of patients; 14 (40%) were coded as other or unknown. The urea reduction ratio, an index of delivered dialysis intensity, was 70.6 ± 7.2%, calculated Kt/V was 1.59 ± 0.41. Estimated daily energy and protein intake were 1,608 ± 621 kCal (mean, 22 kCal/kg) and 61.9 ± 25.6 g (mean, 0.9 g/kg), respectively. Relevant laboratory variables and components of body composition are summarized in Table 1.

Body Composition Analysis
Figure 2 shows the scatter plot of the calculated (DEXA/NaBr) BCM versus BCM derived from BIA (r = 0.92, P < 0.0001) with 95% regression prediction limits and 95% confidence limits. Figure 3 shows the scatter plot of TBW determined from D₂O dilution versus TBW derived from BIA (r = 0.96, P < 0.0001) with 95% regression prediction limits and 95% confidence limits. The ECW/TBW ratio was inversely correlated with the Xc/R ratio derived from BIA (r = −0.73, P < 0.0001, graph not shown). The calculated BCM was 32.0 ± 9.2 kg (range, 20.4 to 57.4 kg) compared with 28.2 ± 6.4 kg (range, 19.5 to 43.1 kg) estimated by BIA (P < 0.0001). The BW derived from D₂O dilution was 40.6 ± 10.3 kg compared with 37.1 ± 9.5 kg estimated by BIA (P < 0.0001). Figures 4 and 5 show the Bland-Altman plots of BCM and TBW, respectively. Figure 4 shows a modest systematic underestimation of BCM by BIA compared with BCM calculated from DEXA/NaBr. Regression adjustment for the two parameters was Y = 1.35X - 3.84. There was excellent agreement in TBW measurement (Figure
TABLE 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age (yr, range)</td>
<td>55.3 ± 11.8 (36 to 75)</td>
</tr>
<tr>
<td>Sex (% female, N)</td>
<td>53% (18)</td>
</tr>
<tr>
<td>Race (%, N)</td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>53% (18)</td>
</tr>
<tr>
<td>White or Latino</td>
<td>47% (16)</td>
</tr>
<tr>
<td>Primary Renal Disease (%, N)</td>
<td></td>
</tr>
<tr>
<td>Diabetic</td>
<td>24% (8)</td>
</tr>
<tr>
<td>Nephrosclerosis</td>
<td>12% (4)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>12% (4)</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>12% (4)</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>40% (14)</td>
</tr>
<tr>
<td>Years on Dialysis (yr, range)</td>
<td>4.3 ± 5.4 (0.2 to 22.8)</td>
</tr>
<tr>
<td>Previous Transplant (% , N)</td>
<td>5% (2)</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>72.1 ± 17.9</td>
</tr>
<tr>
<td>Bone mass (kg)</td>
<td>2.15 ± 0.63</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>24.3 ± 10.7</td>
</tr>
<tr>
<td>LBM (kg)</td>
<td>45.1 ± 11.5</td>
</tr>
<tr>
<td>TBW (kg)</td>
<td>40.6 ± 10.3</td>
</tr>
<tr>
<td>ECW (kg)</td>
<td>13.7 ± 2.8</td>
</tr>
<tr>
<td>ECW/TBW (range)</td>
<td>0.34 ± 0.04 (0.27–0.45)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>25.5 ± 4.5</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.92 ± 0.24</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>11.9 ± 2.3</td>
</tr>
<tr>
<td>Transferrin (mg/dL)</td>
<td>213.1 ± 55.2</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>169.1 ± 40.1</td>
</tr>
<tr>
<td>CO₂ (mEq/L)</td>
<td>20.4 ± 2.5</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>32.1 ± 3.6</td>
</tr>
<tr>
<td>Urea Reduction Ratio (%)</td>
<td>70.6 ± 7.2</td>
</tr>
<tr>
<td>Kt/V&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.59 ± 0.41</td>
</tr>
<tr>
<td>Subjective Assessment (% , N)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>62 (21)</td>
</tr>
<tr>
<td>Mild malnutrition</td>
<td>32 (11)</td>
</tr>
<tr>
<td>Moderate or severe</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Dietary Recall</td>
<td></td>
</tr>
<tr>
<td>Energy (kCal/day)</td>
<td>1608 ± 621</td>
</tr>
<tr>
<td>Protein (g/day)</td>
<td>61.9 ± 25.6</td>
</tr>
</tbody>
</table>

<sup>a</sup> Based on the following equation (47): Kt/V = -1.309 x In (1-URR/102.07), where URR is the urea reduction ratio.

5), requiring little regression adjustment (Y = 1.04X + 1.64).

Test-Retest Reliability

Test-retest reliability was assessed by the coefficients of variation of repeated BIA tests. When both outpatient dialysis unit measurements were considered, the coefficients of variation were 0.6 and 2.4% for BCM and TBW, respectively. When all three BIA measurements were considered, the coefficients of variation were 3.9 and 4.3% for BCM and TBW, respectively, probably reflecting components of operator-dependent (interobserver) random measurement error, as well as true variation related to test conditions and day-to-day differences in body water (vide supra).

Correlation with Alternative Methods of Nutritional Assessment

BCM estimated by BIA and adjusted for body weight (BIA BCM%) was compared with alternative methods of nutritional assessment. The BIA BCM% was 37.2 ± 5.6% (range, 27.3 to 46.6%). There was an inverse correlation between BIA BCM% and total cholesterol (r = -0.43, P = 0.01). There were no significant correlations among BIA BCM% and subjective global assessment (r = 0.08, P = 0.66), dietary energy intake (r = 0.20, P = 0.25), dietary protein intake (r = -0.08, P = 0.67), serum albumin (r = 0.14, P = 0.45), creatinine (r = 0.18, P = 0.30), transferrin (r = -0.06, P = 0.78), bicarbonate (r = 0.07, P = 0.69), and hematocrit (r = -0.14, P = 0.43). Within this small sample, however, there was little correlation among any of the alternative measures (data not shown).
Differences in TBW with the actual volume calculated estimated ultrafiltration by an average of 1 mm of dialysis completion.

**DISCUSSION**

The study of BIA in ESRD has been ongoing for several years. Although the technique has been thoroughly validated in the estimation of TBW (35), only recently have efforts been made to investigate the role of BIA in nutritional assessment in this population. Kurtin et al. (36) used BIA in a study of 19 patients with renal disease (10 patients on hemodialysis, 5 patients on peritoneal dialysis, and 4 patients with chronic renal insufficiency) and compared their results with nonuremic historical controls. The authors noted that hemodialysis patients had reduced LBM compared with other groups and that BIA predicted body fat as determined by anthropometry. Dumler and coworkers (37) evaluated BIA in stable hemodialysis patients monitored over several months’ time. In that study, BIA discriminated among underweight and overweight persons in terms of fat mass, LBM, and TBW, with anthropometry as the gold standard. Serial body weight measurements did not correlate with BIA, which suggested reductions in LBM in several subjects whose body weight was unchanged. More recently published reports also compared BIA with anthropometry and suggested that BIA might be a valid and reliable indicator of body composition and useful in nutritional assessment (38–40).

Although pioneering, these previous studies were limited in several important respects. First, fat-free or LBM, rather than BCM, was the focus of body composition analysis, with increasing LBM% indicating a superior nutritional state. Although more sensitive as an indicator of nutrition than body weight alone, LBM by definition includes ECW, a body compartment typically increased in patients with ESRD and other debilitating chronic diseases (20). Therefore, a reduction in visceral and/or somatic protein mass might be masked by concomitant accumulation of “lean” ECW.

Second, most studies have used anthropometry as the standard of comparison for nutritional assessment. Although widely used in populations with normal renal function, anthropometry is operator dependent, and results may be misleading in dialysis-dependent patients because of altered tissue turgor. Some investigators have suggested that anthropometry markedly underestimates the degree of protein loss in ESRD (41). Last, mathematical agreements between BIA and other methods of body composition, with statistical techniques other than correlation analyses, have not been routinely assessed.

The ability to predict TBW and the ECW/TBW ratio are favorable properties of BIA. An accurate, reliable, and direct measure of TBW might assist the nephrologist in the dialysis prescription, with regard to the need for ultrafiltration, as well as in the estimation of the volume of distribution of urea, which is applicable to kinetic modeling (the V of Kt/V). Most available equations used to estimate body water (e.g., using height and body weight) were derived from nonuremic populations and may not provide accurate estimates in ESRD patients. In our subjects, we compared the Hume and Weyers formula (42) with TBW by D_2O. Body water was underestimated in 29 of 33 subjects; the correlation coefficient was 0.92, compared with
0.96 with BIA. Results were similar using the Watson approximation (43). It should be noted that the assessment of TBW by BIA immediately postdialysis overestimates the actual volume of ultrafilter removed, so that predialysis or delayed (at least 30 min) postdialysis measurements should be used.

The prediction of ECW/TBW might also prove to be helpful, given the morbidity associated with extracellular volume excess and interstitial edema. Although the correlation coefficient between Xc/R and ECW/TBW (r = 0.73) was lower than that between Ht²/R and TBW (r = 0.96), reduced variability in the ratio (0.34 ± 0.04) compared with TBW alone (40.6 ± 10.3) attenuates the magnitude of the correlation coefficient and understates the relative strength of the relationship. The use of multifrequency BIA may further improve the prediction of ECW/TBW compared with the Xc/R ratio (35,44,44a).

The estimation of BCM may prove to be the most valuable aspect of BIA. At present, by relying largely on physical examination and serum proteins, nephrologists and other practitioners may be underdiagnosing malnutrition or detecting it late in the course of disease. It remains to be seen whether the use of BIA will allow more prompt identification of malnutrition. However, focusing on BCM rather than body weight is likely to help—it is well known that reductions in BCM are associated with increased susceptibility to infection and additional physiologic impairments and that those in excess of 25 to 30% are incompatible with life. Perhaps a 5 to 10% reduction in BCM, if identified early, could be reversed with appropriate interventions, before irreversible damage (e.g., infection, further catabolism) occurs.

There are several explanations as to why the correlation among different measures of nutritional assessment was low. The sample variance of albumin, creatinine, and other laboratory test values was relatively low, as was the sample size, thereby reducing the likelihood of demonstrating statistically significant correlations. Likewise, there were few patients with moderate or severe malnutrition, at least by subjective assessment. An additional, and plausible, explanation is that BIA and other methods of body composition analysis capture a different dimension of nutritional status, other than what can be explained by the level of serum albumin or dietary protein intake, for instance.

There are important limitations to this study. First, the standards of comparison were imperfect, and in the case of BCM, variation in the two component measurements, DEXA and NaBr, is additive. Second, few study participants were thought to have moderate or severe malnutrition by subjective assessment. The baseline anthropometric and laboratory characteristics (e.g., mean body weight, 72.2 kg; mean serum albumin, 3.92 g/L) support this contention. Nevertheless, there is no reason to believe that BIA would be less valid in persons of lower body weight or BCM. Last, no patients on peritoneal dialysis were included, which limits generalizability. Previous studies have suggested that BIA is unable to detect acute changes in peritoneal fluid volume (45), although the estimation of BCM should not be severely affected.

In summary, using BCM as a nutritional surrogate, we showed direct correlation between BCM estimated by BIA and BCM determined by DEXA and NaBr dilution. As expected, there was strong correlation between TBW estimated by BIA and TBW determined by D₂O dilution. Repeated BIA measurements performed by various dialysis unit personnel showed excellent reproducibility. On the basis of the results presented above, we believe that BIA is a valid and reliable method of nutritional assessment in maintenance hemodialysis patients. Serial tests over time to assess sensitivity to change and association with relevant outcomes, such as survival, hospitalization rate, vitality, and functional status, will be required to better define the role of this technology.

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