Four-component model of body composition in chronic renal failure comprising dual-energy X-ray absorptiometry and measurement of total body water by deuterium oxide dilution

Graham WOODROW, Brian OLDROYD*, John H. TURNER, Peter S. W. DAVIES†‡, Janice M. E. DAY† and Michael A. SMITH*
(Received 5 June/22 July 1996; accepted 2 August 1996)

INTRODUCTION

Techniques of body composition analysis allow measurement of different components of the human body, divided according to physical properties [1–3]. Body composition analysis now plays an important role in a wide range of areas of biological research including the study of nutrition, exercise physiology and normal human physiological changes such as growth and ageing. Subjects suffering from advanced chronic renal failure (CRF) often suffer from malnutrition and this is a major factor in the increased morbidity and mortality that occurs in these patients. A number of studies over many years have investigated nutritional status in CRF using a variety of body composition techniques [4–11].

Techniques may be used alone or in combination, to divide the composition of the human body into models of varying complexity [3, 12–14]. These models rely on assumptions regarding body composition, which may constitute a major source of error, particularly when measurements are made in

Key words: body composition, chronic kidney failure, densitometry, X-ray absorptiometry, total body water.
Abbreviations: ANOVA, analysis of variance; CRF, chronic renal failure; DEXA, dual-energy X-ray absorptiometry; FFM, fat-free mass; TBF, total body fat; TBK, total body potassium; TBW, total body water.
‡Present address: School of Human Movement Studies, Faculty of Health, Queensland University of Technology, Kelvin Grove Campus, Brisbane, Queensland, Australia.
Correspondence: Dr G. Woodrow, Renal Unit, The General Infirmary at Leeds, Great George Street, Leeds LS1 3EX, U.K.
subjects suffering from pathological conditions which make deviation from the assumptions regarding body composition more likely.

The two-compartment model is the basis of many body composition methods, including densitometry, bioelectrical impedance and skinfold anthropometry. This model divides body mass into total body fat (TBF) and the remaining fat-free mass (FFM). Whereas fat is relatively homogenous in composition, FFM is a very heterogeneous entity, consisting predominantly of water (which is believed to be present exclusively in the FFM compartment), protein and minerals. Techniques based on the two-compartment model assume that all elements are present in constant proportions in all individuals. This is not the case even in normal subjects, where some variability in the water content of the FFM has been demonstrated [14]. It would be expected to be particularly unlikely in CRF, where abnormalities of salt and water balance are a major feature of the disease. In patients with CRF not receiving dialysis, fluid retention or dehydration may occur. In patients with CRF receiving dialysis, fluid balance is manipulated by the degree of fluid removed by the dialysis procedure, which is estimated by the clinician on the basis of fairly imprecise criteria. The presence of renal osteodystrophy, with loss of bone mineral, may represent another source of error.

As potassium is found in the fat-free body tissues, being the major intracellular cation, measurement of total body potassium may allow estimation of FFM. However, abnormalities of potassium metabolism in uraemia may affect the validity of this method in patients with CRF, with one study suggesting a reduction of the content of potassium per unit mass of fat-free tissue [15]. Measurement of total body nitrogen by neutron activation analysis can allow direct assessment of body protein content with a high degree of precision, without relying on the assumptions made by the other techniques described [5–8]. Although it is a potentially valuable research tool in the study of patients with CRF, its use is limited by the very small number of centres worldwide where it is available, and by the exposure of patients to ionizing radiation.

Dual-energy X-ray absorptiometry (DEXA) allows direct measurement of body fat, lean tissue and bone mineral without making the assumptions of the two-compartment model [16, 17]. The attenuation of saline is very similar to that of lean tissue measured by DEXA, so changes in hydration are perceived by DEXA as changes in lean tissue [9, 18, 19]. Thus the degree of hydration should not affect the validity of the estimation of the three compartments measured by DEXA. However, as it does not distinguish between water and protein, when the lean tissue compartment is affected by abnormalities in salt and water metabolism as occur in CRF, the value of lean tissue measured by DEXA as a measure of protein nutritional status will be reduced.

The purpose of this study was to use a combination of DEXA and measurement of total body water (TBW) by deuterium oxide dilution (\(^{2}H_{2}O\)) to determine the variability of hydration in groups of patients with CRF compared with normal subjects, and to assess the ability of this combination of techniques to estimate body protein stores from a four-component model consisting of fat, protein, TBW and body mineral.

**METHODS**

We studied four groups of subjects, including patients with advanced CRF not yet on dialysis, patients on peritoneal dialysis, patients on haemodialysis, and a group of healthy control subjects. The undialysed CRF patients were selected from patients undergoing regular follow-up in outpatient clinics and had advanced CRF (serum urea >30 mmol/l or creatinine >500 μmol/l). Peritoneal dialysis patients included 21 subjects undergoing standard continuous ambulatory peritoneal dialysis (three or four exchanges of 1.5 to 2.5 l of dialysate per day) and three receiving nocturnal intermittent peritoneal dialysis. They had been receiving dialysis for a median time of 25 (range 5 to 109) months and had a mean weekly \(K_t/V\) (urea) of 2.1 (0.7). Haemodialysis patients received either two sessions (eight patients) or three sessions (12 patients) of 4 h of dialysis per week, using bicarbonate buffered dialysate and cuprophane membrane dialysers. Mean \(K_t/V\) (urea) was 1.62 (0.27) per dialysis for those dialysed twice weekly and 1.31 (0.23) for those dialysed three times per week. They had been receiving dialysis for a median time of 14 (range 6 to 41) months. Control subjects were recruited from patients’ spouses, hospital employees and sources outside the hospital and were free from any significant medical problems. All subjects were Caucasian and none had diabetes. Patients suffering significant acute illness (including continuous ambulatory peritoneal dialysis peritonitis) within the previous 3 months were also excluded. Subjects were randomly selected from groups of subjects of similar ages, meeting the study entry criteria. Measurements in patients on dialysis were performed within 1 h of finishing a dialysis session for patients on haemodialysis, and with a ‘dry’ peritoneal cavity after drainage of peritoneal dialysate in patients on peritoneal dialysis. Hydration of the subjects was felt to be close to ‘normal’ on clinical assessment. Patient characteristics are shown in Table 1.

DEXA was performed using a Lunar DPX-L absorptiometer (Lunar Radiation Corporation, Madison, WI, U.S.A.). Whole-body scans were performed at the scan speed suggested by the system for the particular subject. Analysis was by version 1.3 total body software, using the extended research
Body composition in chronic renal failure

Table 1. Characteristics of study subjects. Comparisons of means of CRF groups with control groups by ANOVA. NS, not significant.

<table>
<thead>
<tr>
<th></th>
<th>Control subjects (n = 34)</th>
<th>Peritoneal dialysis patients (n = 21)</th>
<th>Undialysed CRF patients (n = 20)</th>
<th>Haemodialysis patients (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>17/17</td>
<td>10/11</td>
<td>10/10</td>
<td>10/10</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>59.0 (6.8)</td>
<td>60.0 (19.6) NS</td>
<td>56.7 (13.3) NS</td>
<td>61.2 (10.3) NS</td>
</tr>
<tr>
<td>Female</td>
<td>57.0 (8.8)</td>
<td>55.9 (13.5) NS</td>
<td>51.7 (17.9) NS</td>
<td>62.0 (11.8) NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>171.0 (5.7)</td>
<td>169.9 (7.9) NS</td>
<td>169.8 (6.9) NS</td>
<td>166.7 (6.9) NS</td>
</tr>
<tr>
<td>Female</td>
<td>162.2 (7.7)</td>
<td>155.9 (6.1) P&lt;0.05</td>
<td>157.0 (6.4) NS</td>
<td>156.8 (6.9) NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>76.5 (9.5)</td>
<td>73.3 (15.0) NS</td>
<td>71.2 (11.5) NS</td>
<td>66.6 (7.2) P&lt;0.01</td>
</tr>
<tr>
<td>Female</td>
<td>65.4 (12.5)</td>
<td>58.3 (11.5) NS</td>
<td>59.1 (13.0) NS</td>
<td>53.9 (13.0) P&lt;0.05</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26.2 (3.3)</td>
<td>25.2 (3.6) NS</td>
<td>24.7 (3.6) NS</td>
<td>24.0 (2.5) NS</td>
</tr>
<tr>
<td>Female</td>
<td>24.8 (3.6)</td>
<td>24.0 (4.5) NS</td>
<td>24.0 (5.4) NS</td>
<td>21.8 (4.0) NS</td>
</tr>
</tbody>
</table>

Analysis mode. FFM was derived from the sum of lean tissue and bone mineral content estimated by DEXA.

TBW was determined by deuterium oxide (D₂O) dilution using saliva samples. A baseline saliva sample was collected, then an oral solution of 10% D₂O was administered at a dose of approximately 0.05 g D₂O/kg body weight. The exact administered dose was calculated by weighing the dosing container before and after administration on a balance with a precision of 0.01 mg. Two further saliva samples were then collected between 3 and 6 h after administration of the D₂O. The isotope ratio of deuterium in the saliva samples and in the administered dose was determined by mass spectrometry and TBW was calculated by the ‘plateau’ method [20], which assumes complete equilibration of the administered dose of D₂O throughout the TBW space at the time of the second saliva sample. The value for TBW thus obtained was then divided by a factor of 1.04 to correct for exchange of deuterium with non-aqueous hydrogen in the body [21]. The coefficient of variation of repeated measurements of isotopic enrichment in saliva is less than 0.5%.

A four-component model of body composition was derived from the combination of DEXA and TBW, consisting of fat, protein, TBW and body mineral. Fat was estimated directly by DEXA and TBW from D₂O dilution. Body mineral was derived from the DEXA estimate of total body bone mineral multiplied by a factor of 1.274 [14]. Protein was derived from the equation:

\[
\text{Protein} = \text{FFM} - \text{TBW} - \text{total body mineral}
\]

(where FFM is the sum of lean tissue and bone mineral content estimated by DEXA).

Body hydration was derived from the equation:

\[
\text{Hydration (\%)} = \frac{\text{TBW} \times 100}{\text{FFM}}
\]

In addition, total body potassium (TBK) was measured in the normal control subjects (male 132.99 g, SD 16.99; female 95.86 g, SD 15.63). This was done by measuring γ-ray emissions from the naturally occurring ⁴⁰K isotope of potassium present in the body. This was done using an eight detector whole-body counter. FFM was estimated by the equation of Morgan et al. [22]:

\[
\text{FFM (kg)} = 8.88 + \frac{\text{TBK (mmol)}}{70}
\]

Total body nitrogen was calculated from TBK by the following equation [22] and total body protein was estimated as 6.25 times total body nitrogen:

\[
\text{Total body nitrogen (g)} = \left(\text{TBK (mmol)} + 1.69\right) / 1.81
\]

Total body protein was also estimated from the anthropometric equation of Burkinshaw et al. [23], and as 27% of DEXA FFM minus total body mineral.

Comparison of means of groups of measurements was performed by analysis of variance (ANOVA) with comparison of patient groups with control subjects, allowing for the effect of multiple comparisons. Correlations were calculated by the Pearson correlation coefficient. Comparison of the estimation of total body protein by different methods was by the method of Bland and Altman [24]. All mean values are expressed as mean (SD).

The study was approved by the hospital ethics committee and all subjects gave informed consent.

RESULTS

TBW is expressed as a percentage of FFM (estimated by DEXA) in Fig. 1. The mean values in the CRF groups did not differ significantly from
those of control subjects (except the female undialysed CRF group). Furthermore, the variability of this estimate of hydration of FFM (as judged by the SDs of these measurements) did not differ between CRF groups and healthy control subjects. Correlations were performed of TBW expressed as a percentage of FFM (estimated by DEXA) with age and percentage TBF (estimated by DEXA). The hydration of the FFM thus calculated was not correlated with age. It was significantly correlated with percentage TBF in the control groups (male \( r = 0.68, P < 0.005 \); female \( r = 0.55, P < 0.05 \)), but not in the CRF groups. Measurements of DEXA whole-body lean tissue are shown in Fig. 2. Compared with the control group, significant reductions in lean tissue were found in both the male and female haemodialysis groups and the female peritoneal dialysis group.

Body composition derived from the four-component model is shown in Table 2. This model showed no differences between estimated body protein in the CRF patients (except female undialysed CRF patients) compared with control subjects, failing to reflect the other abnormalities of lean tissue identified by DEXA whole-body lean tissue estimates. There was a strong correlation of total lean tissue estimated by DEXA with FFM estimated by TBK in control subjects (males \( r = 0.92, P < 0.0001 \); female

---

**Table 2. Body composition estimated from four-component model.** Comparisons of CRF groups with the control groups by ANOVA. NS, not significant.

<table>
<thead>
<tr>
<th></th>
<th>Control subjects</th>
<th>Peritoneal dialysis patients</th>
<th>Undialysed CRF patients</th>
<th>Haemodialysis patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td>19.72 (7.73)</td>
<td>19.85 (7.08)</td>
<td>14.47 (8.67)</td>
<td>16.44 (7.55)</td>
</tr>
<tr>
<td>Water</td>
<td>39.66 (3.37)</td>
<td>38.51 (9.21)</td>
<td>40.27 (3.38)</td>
<td>35.42 (4.67)</td>
</tr>
<tr>
<td>Body mineral</td>
<td>3.55 (0.39)</td>
<td>3.28 (0.62)</td>
<td>3.24 (0.43)</td>
<td>3.36 (0.54)</td>
</tr>
<tr>
<td>Protein</td>
<td>13.61 (3.40)</td>
<td>11.47 (2.99)</td>
<td>13.47 (4.56)</td>
<td>11.68 (2.95)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td>21.68 (8.62)</td>
<td>20.16 (10.74)</td>
<td>18.52 (11.62)</td>
<td>16.70 (9.37)</td>
</tr>
<tr>
<td>Water</td>
<td>31.15 (4.55)</td>
<td>26.53 (2.86)</td>
<td>30.98 (3.38)</td>
<td>27.06 (3.77)</td>
</tr>
<tr>
<td>Body mineral</td>
<td>2.97 (0.54)</td>
<td>2.26 (0.56)</td>
<td>2.43 (0.61)</td>
<td>2.15 (0.38)</td>
</tr>
<tr>
<td>Protein</td>
<td>9.18 (2.85)</td>
<td>8.86 (2.05)</td>
<td>6.90 (2.74)</td>
<td>7.69 (1.16)</td>
</tr>
</tbody>
</table>
Body composition in chronic renal failure

$r = 0.89, P < 0.0001$), and a similarly strong correlation of FFM estimated by DEXA and FFM estimated by TBK in control subjects (male $r = 0.91, P < 0.0001$; female $r = 0.89, P < 0.0001$). However, protein estimated by the four-component model was much less strongly correlated with FFM from TBK in male control subjects ($r = 0.51, P < 0.05$) and not significantly correlated in the female control subjects ($r = 0.38, P$ not significant). Body protein estimated simply as $27\%$ of DEXA FFM minus total body mineral (i.e. assuming constant hydration of the fat-free compartment of $73\%$) showed a much closer agreement to that estimated by TBK than did protein estimated by the combined DEXA and TBW model (Fig. 3). Estimating protein from $27\%$ of DEXA FFM minus total body mineral was more sensitive than the four-component model in detecting protein depletion, with reduced body protein being demonstrated in both haemodialysis groups (Table 3). Mean body protein estimated by the four-component model, as $27\%$ of DEXA FFM minus total body mineral and from estimates based on age and height for the study groups did not differ except in the male control subjects (Table 3).

**DISCUSSION**

Nutritional assessment is of crucial importance in the management of patients with CRF. Malnutrition is common in CRF and is a major adverse prognostic factor [25–28]. Malnutrition may be difficult to treat in these patients and its early detection and treatment could be of great clinical importance. The wide variety of physical and biochemical methods of nutritional assessment that have been described and are used in clinical practice is evidence in itself that none is without significant problems, particularly when applied to patients with CRF [29].

![Fig. 3. Bland and Altman comparisons of protein estimated in normal control subjects by the four-component model and 27% DEXA FFM minus body mineral, using protein estimated by TBK as the criterion method](image)

**Table 3. Total body protein derived from the four-component model, as 27% of DEXA FFM minus total body mineral and from age and height (Burkinshaw et al. [23]). Comparisons of estimates by different methods by ANOVA. NS, not significant.**

<table>
<thead>
<tr>
<th>Total body protein (kg)</th>
<th>Four-component model</th>
<th>27% DEXA FFM minus body mineral</th>
<th>Age and height [23]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control subjects</td>
<td>13.61 (3.40)</td>
<td>11.79 (1.10)</td>
<td>12.08 (0.75)</td>
</tr>
<tr>
<td>Peritoneal dialysis patients</td>
<td>11.47 (2.99)</td>
<td>11.10 (1.82)</td>
<td>11.92 (1.04)</td>
</tr>
<tr>
<td>Undialysed CRF patients</td>
<td>13.47 (4.56)</td>
<td>12.07 (1.82)</td>
<td>11.91 (0.90)</td>
</tr>
<tr>
<td>Haemodialysis patients</td>
<td>11.68 (2.95)</td>
<td>10.27 (1.79)*</td>
<td>11.51 (0.91)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control subjects</td>
<td>9.24 (2.78)</td>
<td>8.72 (1.23)</td>
<td>8.62 (1.06)</td>
</tr>
<tr>
<td>Peritoneal dialysis patients</td>
<td>8.86 (2.05)</td>
<td>7.91 (0.95)</td>
<td>7.72 (0.79)</td>
</tr>
<tr>
<td>Undialysed CRF patients</td>
<td>6.90 (2.74)</td>
<td>6.45 (0.94)</td>
<td>7.85 (0.84)</td>
</tr>
<tr>
<td>Haemodialysis patients</td>
<td>7.69 (1.16)</td>
<td>7.81 (1.08)*</td>
<td>7.83 (0.90)</td>
</tr>
</tbody>
</table>

*Estimates of body protein as 27% of DEXA FFM minus total body mineral were significantly lower in the haemodialysis groups than in the control subjects (both $P < 0.05$), but not in the other CRF groups.
Abnormalities in hydration are a major confounding factor in the clinical assessment of nutritional status of patients with CRF. In undialysed patients, the effect of changes in hydration on body weight can mask the effect of changes in protein or fat stores. In patients on dialysis, fluid is removed to maintain body weight at a clinically determined ‘dry weight’. Very significant increases or decreases in protein and fat stores may then occur before the resulting relative fluid depletion or overload becomes clinically apparent. Abnormalities of hydration may also play a major part in causing inaccuracy of body composition techniques when applied to patients with CRF. It is thus gratifying that in the groups of CRF patients in this study, who were clinically thought to be at an ‘ideal’ state of fluid balance, hydration (TBW by $2\text{H}_2\text{O}$ dilution as a percentage of FFM determined by DEXA) was similar to control subjects both in terms of means and SDs of results. This does not, however, imply similar fluid distribution between different compartments. This could be affected by various factors including the frequent presence of cardiovascular disease in patients with CRF and the effects of dialysis and could be of particular importance with respect to the validity of bioelectrical impedance in these patients [30]. Increased TBW (especially extracellular fluid) has been shown to be related to increased fat stores [31], and in this study we demonstrated a correlation between hydration of the FFM and percentage TBF in the normal subjects. This relationship was not demonstrated in the patients with CRF, however, where other factors related to renal failure and dialysis may be of greater importance in determining body water content.

It was hypothesized that variable hydration in patients with CRF may reduce the ability of DEXA estimates of lean tissue (which is composed mainly of water and protein) to reflect protein nutritional status. Thus, combining DEXA and TBW to derive an estimate of protein independent of hydration would result in greater sensitivity in the detection of protein depletion. However, we found that this model was unable to detect abnormalities which were detected by DEXA lean tissue measurement alone. Furthermore, the four-component model estimate of protein correlated poorly with FFM estimated by TBK in normal subjects, whereas DEXA lean tissue alone showed a high correlation. Estimating protein from DEXA alone, as a fixed proportion of DEXA FFM minus body mineral, showed much closer agreement to TBK estimates of body protein than did the combined DEXA TBW model.

Body water is the major constituent of the FFM. One problem in the indirect estimation of body protein from the combined DEXA and TBW model is that extrapolation of relatively small errors in either or both of the estimates of FFM and TBW will result in proportionally much larger errors in the estimate of the smaller protein component. These errors may be of greater significance than the effect of variable hydration on the use of DEXA estimates of lean tissue as a marker of protein nutritional status. Substances other than protein are present in the anhydrous component of lean tissue, principally glycogen and nucleic acids, and these may slightly exaggerate estimates of body ‘protein’ derived from the four-component model.

Although variable hydration is a potential source of error in the assessment of the nutritional status in CRF, in groups of patients clinically thought to have normal fluid balance, hydration may be equivalent to that found in a normal population. DEXA is a valuable addition to the list of methods available for nutritional assessment and body composition analysis. A potential problem with multi-compartment models is inaccuracy due to the propagation of errors of measurement techniques. A four-component model of body composition derived from the combination of TBW with DEXA actually reduces the validity of DEXA alone for assessment of protein nutritional state because of the combination of errors associated with the methods used for indirect estimation of body protein by this model. As hydration in the CRF patients studied was not dissimilar to that of healthy control subjects, it is possible that this four-component model designed to overcome the effects of variable hydration on body composition assessment could be of greater utility in subjects with marked derangement of body fluid content. This could explain why the four-component model detected protein depletion only in the female undialysed CRF group, who were the only group found to have significant abnormalities of body hydration.

REFERENCES