Bioelectrical impedance can be used to predict muscle mass and hence improve estimation of glomerular filtration rate in non-diabetic patients with chronic kidney disease

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Abstracts

Background. In this article (the second of two companion studies), we report whether bioelectrical impedance analysis (BIA) can be used to predict muscle mass in patients with chronic kidney disease (CKD), and whether using this predicted muscle mass can improve the estimation of glomerular filtration rate (GFR).

Methods. Seventy five non-diabetic patients with CKD (mean age ± SD, 65.1 ± 12.0 years; mean GFR 45.9 ± 28.8 ml/min/1.73 m²) underwent body composition analysis by dual energy X-ray absorptiometry to provide a criterion marker of skeletal muscle mass (appendicular lean mass, ALM). Validity of a published BIA equation to predict ALM was evaluated and a new BIA equation was generated (ALMBIA) and cross-validated by the leave-one-out procedure. Renal inulin clearance provided a criterion measure of GFR (GFR inulin). The performance of the equation including ALMBIA to estimate GFR inulin was compared with demographic variables as used in the modification of diet in renal disease (MDRD) equation, by determining bias, limits of agreement and accuracy.

Results. The previously published BIA equation to predict ALM was not valid in these patients with CKD. In contrast, our new ALMBIA equation was generated and cross-validated by the leave-one-out procedure. Renal inulin clearance provided a criterion measure of GFR (GFR inulin). The performance of the equation including ALMBIA to estimate GFR inulin was compared with demographic variables as used in the modification of diet in renal disease (MDRD) equation, by determining bias, limits of agreement and accuracy.

Results. The previously published BIA equation to predict ALM was not valid in these patients with CKD. In contrast, our new ALMBIA equation was generated and cross-validated by the leave-one-out procedure. Compared with the MDRD demographic variables, using ALMBIA to predict GFR inulin improved estimation performance, showing reduced bias (4.3 vs 15.6 ml/min) and improved limits of agreement (41.1 vs 59.2 ml/min) and accuracy (69.7 vs 39.4% of patients’ predicted GFR did not deviate by more than 30% of GFR inulin).

Conclusions. ALMBIA provides a clinically obtainable and valid method to predict muscle mass in patients with CKD, and using ALMBIA improves the estimation of GFR inulin. Researchers developing future GFR estimation equations should consider including ALMBIA.

Keywords: Bioelectrical impedance; body composition; creatinine; glomerular filtration rate; MDRD; muscle mass

Introduction

‘A non-invasive and accurate estimation of GFR is one of the holy grails of nephrology’, p. 2573 [1].

Current criterion methods to predict glomerular filtration rate (GFR) are invasive, time consuming, expensive and technically difficult. Consequently GFR is usually estimated by equations that utilize serum creatinine and anthropometric and demographic variables (such as the modification of diet in renal disease (MDRD) equation [2]). However, GFR estimation by these equations is often inaccurate, especially in patients with abnormal body composition. For example, Vervoort et al. [3] noted that the MDRD formula underestimated GFR in diabetic patients ‘…due to changes in body composition’ (p. 1913). We believe this is because muscle mass mediates the relationship between demographic/anthropometric variables and GFR. In a companion article to the present study, we provide evidence to suggest that demographic/anthropometric variables are included in GFR estimation equations primarily...
because they predict muscle mass, the source of serum creatinine [4]. However, because demographic/anthropometric variables fail to take into account individual variability in muscle mass, their inclusion alone may lead to inaccuracy in GFR estimation [5,6]. Data concerning whether including more direct markers of muscle mass will improve GFR estimation is currently equivocal [6,7].

In any case, before GFR estimation equations utilizing muscle mass can be implemented in clinical practice, quick, simple and cheap methods to measure muscle mass must be validated for chronic kidney disease (CKD) patients. Furthermore, clinically obtainable measures of muscle mass would be useful in applications other than GFR estimation, as muscle mass also predicts functional capacity, quality of life and outcome in CKD [8]. Although regular monitoring of nutritional status of CKD patients is recommended by the National Kidney Foundation–Kidney Disease Outcomes and Quality Initiative (KDOQI), clinically applicable methods to monitor nutritional status remain elusive.

Opinion remains divided as to the best method for measuring muscle mass in patients with CKD because of the complication of altered hydration status in this population. Although we [4] and others [6,9] have shown that including muscle mass by techniques such as dual energy X-ray absorptiometry and computed tomography improve GFR estimation, these methods are unlikely to be available for the large number of GFR estimations needed in clinical practice. In contrast, bioelectrical impedance analysis (BIA) shows promise by providing cheap and quickly obtainable measures of body composition even with non-skilled operators, and has been extensively used in healthy persons [10] and to a lesser extent in those with CKD [11]. Accordingly, Kyle et al. [12] developed an equation to estimate muscle mass in 444 healthy persons using BIA, and validated it on 326 pre- or post-heart, lung or liver transplant patients. This equation is particularly attractive because it specifically predicts appendicular lean mass (ALM), the variable that we identified in our companion article as important in explaining variance in GFR [4]. Some studies, however, show poor validity of the bioelectrical impedance technique in CKD patients, in part due to the use of population specific regression equations that may not be applicable in states of fluid overload and altered body composition [11]. Furthermore, Kyle et al. [12] excluded patients with CKD and fluid abnormalities, and no studies have yet evaluated validity of this equation in the CKD population.

Thus the aims of the present study, the second of two related studies using muscle mass to estimate GFR, were to test the validity of the Kyle et al. [12] equation to predict muscle mass from bioelectrical impedance in patients with CKD, and should validity of this equation be poor, to develop and validate a new CKD-specific prediction equation. Ultimately, we sought to determine if using predicted muscle mass by bioelectrical impedance could improve GFR estimation over and above the currently advocated MDRD equation.

**Methods**

As part of a series of studies investigating the use of measured muscle mass to estimate GFR, we recruited 77 non-diabetic subjects attending pre-dialysis clinics at Ysbyty Gwynedd and Glan Clwyd. Of these, 75 subjects had full bioelectrical impedance data available for analysis. Detailed methods are provided elsewhere [4] but are briefly described below with significant changes highlighted. All subjects were >18 years, and had CKD classified as KDOQI stage 1–5. Ethical approval was obtained from the North Central Wales Local Research Ethics Committee, and all participants gave written informed consent.

Patients initially attended their Renal Unit for blood tests and GFR assessment by single shot bolus injection and total body clearance of inulin (GFR\textsubscript{inu}). Within 7 days, patients attended the laboratories of the School of Sport, Health and Exercise Sciences at the University of Wales, Bangor for body composition assessment. As suggested by Kim et al. [13], the criterion method for obtaining a proxy measure of skeletal muscle mass was measurement of ALM by dual energy X-ray absorptiometry (DXA, QDR1500, software version 5.72, Hologic, Waltham, USA). As suggested by Kyle et al. [12], the clinically applicable method for predicting skeletal muscle mass was the measurement of whole body bioelectrical impedance (Hydra ECF/ICF 4200, Xitron Technologies, San Diego, USA). For bioelectrical impedance measures, proximal electrode sites were the dorsal surfaces of the wrist and ankle and the distal sites were the base of the third metacarpo- and metatarsal-phalangeal joints of the hand and foot. Resistance (expressed as height (m)\textsuperscript{2}/resistance) and reactance were recorded at 50kHz to provide markers of soft tissue body composition. Reliability data obtained in our lab on a group of nine patients with end-stage kidney disease tested on two occasions separated by 3 months suggests a coefficient of variation for bioelectrical impedance parameters ranging from 4.1 to 7.4\% [8]. Finally, a measure of hydration status was required to identify overhydrated patients and determine whether fluid retention was associated with the error of the Kyle et al. equation [12] in predicting muscle mass. Due to problems in assessing hydration status using blood pressure or non-quantifiable clinical signs of oedema, the following alternative method was chosen: total body water (measured by bioelectrical impedance) of the fat free mass (by dual energy X-ray absorptiometry) was expressed as a percentage. For comparison, normal values for hydration were obtained from our unpublished observations on healthy individuals (n=31) with similar demographics to the patients of the present study. It should be noted that while this method is valid at a group level, due to propagation of errors of both bioelectrical impedance and dual energy X-ray absorptiometry physiologically implausible results were generated in some individuals, negating this technique as useful on an individual basis.
Statistics

Validity of a bioelectrical impedance equation [12] to predict muscle mass. Firstly, muscle mass (ALM) was predicted using the Kyle et al. [12] equation (ALMKyle), and compared to our criterion measure of muscle mass, dual energy X-ray absorptiometry measured ALM (ALMDXA) by t-test, correlation analysis and Bland–Altman plots detailing the mean difference between predicted and GFRinu (bias), and the limits of agreement [SD of bias × 1.96 (95% confidence interval)].

Generation and cross validation of a new bioelectrical impedance equation to predict muscle mass. Since the validity of predicting muscle mass (ALM) using the Kyle et al. [12] equation (ALMKyle) was shown to be poor (see ‘results’ section), a new equation was generated using the leave-one-out cross-validation method [14]. Leave-one-out cross-validation is an internal validation performed to check the predictive power of the local model that simulates an external validation. Using stepwise regression technique, an equation to predict muscle mass (ALM) is generated on the entire sample minus one observation, which is then tested on the left-out observation. This is repeated such that each observation in the sample is used once as the validation data. The residuals (the difference between the predicted and the observed ALM) are calculated, and the root mean square error is determined, providing an estimate of prediction error in external samples. All observations are included to generate the final equation.

Performance of bioelectrical impedance predicted muscle mass (ALMBIA) to estimate GFR. We have shown elsewhere that muscle mass (ALMDXA) mediates the relationship between commonly used demographic/anthropometric predictor variables and GFR, and that an equation including ALMDXA explained more variance in GFR than these demographic/anthropometric variables alone [4]. In the current study, we present a clinically obtainable and valid equation to predict muscle mass using bioelectrical impedance (see equation ALMBIA in ‘results’ section). A final analysis determined if using this muscle mass prediction (ALMBIA) would improve GFR estimation despite the error associated with predicting muscle mass by bioelectrical impedance. The GFR estimation equation utilizing muscle mass that was developed previously in our companion study [4] was employed, the only difference being that muscle mass was predicted by bioelectrical impedance rather than measured by dual energy X-ray absorptiometry. Performance of this method (GFRBIA) was compared with an equation including demographic variables as utilized by the MDRD formula with constants generated on this data set (GFRdemo). Performance was separately assessed in three groups: the first group (n = 42) had normal body composition; the second group (n = 33) had extreme body composition, i.e. either low or high muscle mass (ALM > ±1SD of our sample mean) or low- or high-fat mass (≥±1SD of our sample mean); and the third group (n = 9), which comprised patients from both of the first two groups, were overhydrated (hydration of the fat free mass > ±2SD of normal values). Performance was assessed by repeated measures ANOVA, simple correlation and standard error of the estimate (SEE) and Bland–Altman Plots. Accuracy was assessed as mean error% and the percentage of results that did not deviate by more than 30 and 50% of GFRinu.

All analyses were performed on a statistical computer package (SPSS version 12, Illinois, USA). Values are expressed as means ± SD. For multiple regression analyses, relevant assumptions including normality, linearity, homoscedasticity and multicollinearity were checked as detailed previously [4]. Data transformations were not required for muscle mass prediction but were required for GFR prediction; however, to enable easy interpretation of performance of GFR estimation equations, data were converted from transformed to raw GFR values.

Results

Patient characteristics have been detailed previously [4]. Briefly, the 75 non-diabetic patients for whom we had bioelectrical impedance data available were aged 65.1 ± 12.0 years, 65.3% were male, were 166.1 ± 9.7 cm tall and weighed 76.9 ± 13.6 kg, had kidney function classified as KDOQI stages 1–5 and a mean GFR of 45.9 ± 28.8 ml/min/1.73 m² (range 14.3–133.2 ml/min/1.73 m²). The hydration (measured by bioelectrical impedance) of the fat-free mass (measured by dual energy X-ray absorptiometry) was 75.9 ± 8.8% compared with 75.0 ± 6.9% (patients vs healthy controls, respectively).

Validity of a bioelectrical impedance equation [12] to predict muscle mass. Bias and limits of agreement of muscle mass predicted by the Kyle et al. [12] equation (ALMKyle) compared with our criterion measure of muscle mass (ALMDXA) equation is shown in Figure 1. There was a significant difference between ALMDXA and ALMKyle (18.7 ± 5.4 kg vs 21.0 ± 4.6 kg, t = 8.210, df = 74, P < 0.001). The correlation between ALMDXA and ALMKyle was significant (r = 0.888, P < 0.001) but the SEE was large (2.49 kg). The bias of ALMKyle was correlated with fat mass (r = 0.679, P < 0.001), hydration of the fat-free mass (r = 0.578, P < 0.001) and ALMDXA (r = −0.525, P < 0.001).

Generation and cross validation of a new bioelectrical impedance equation to predict muscle mass. As validity of ALMKyle was poor in our patient group, a new
where ALM_BIA, predicted ALM using bioelectrical impedance equation (ALMBIA) with actual ALM by dual energy X-ray absorptiometry (ALMDXA). ALMDXA, ALM by dual energy X-ray absorptiometry; ALMBIA, ALM by bioelectrical impedance spectroscopy.  

\[ r = 0.960, \ P < 0.001. \]

Fig. 2. Relationship between predicted ALM using our new bioelectrical impedance equation (ALMBIA) with actual ALM by dual energy X-ray absorptiometry (ALMDXA). ALMDXA, ALM by dual energy X-ray absorptiometry; ALMBIA, ALM by bioelectrical impedance spectroscopy.  

Fig. 3. Bland–Altman plot of predicted ALM using our new bioelectrical impedance equation (ALMBIA) in comparison with actual ALM by dual energy X-ray absorptiometry (ALMDXA). ALMDXA, ALM by dual energy X-ray absorptiometry; ALMBIA, ALM by bioelectrical impedance spectroscopy.  

Performance of bioelectrical impedance predicted muscle mass (ALMBIA) to estimate GFR. Performance was assessed of the following two predictive equations to estimate GFR_{inu}:

\[
\begin{align*}
\text{GFR}_{\text{demo}} \cdot \text{GFR}_{\text{inu}} = & 1.847 + (-0.101 \times \text{Cr}) \\
& + (0.03634 \times \text{age}) \\
& + (-0.454 \times \text{gender})
\end{align*}
\]

\[
\begin{align*}
\text{GFR}_{\text{BIA}} \cdot \text{GFR}_{\text{inu}} = & 1.008 + (-0.104 \times \text{Cr}) \\
& + (0.01644 \times (\text{ALM}_{\text{BIA}})) \\
& + (0.07108 \times \text{weight})
\end{align*}
\]

where GFR_{inu}, log_{10} transformed GFR by inulin clearance (ml/min); Cr, log_{10} transformed serum creatinine concentration (mg/dl); age, k – x transformed age (years); gender, 0 = male, 1 = female; ALM_{BIA}, predicted ALM by bioelectrical impedance (kg); weight, square root transformed weight (kg).

For the full data set, ANOVA revealed a significant difference between GFR_{inu}, GFR_{demo} and GFR_{BIA} (50.3 ± 35.3 vs 40.0 ± 21.8 vs 47.1 ± 24.8 ml/min, respectively, F_{(1.4,104.5)} = 10.572, P < 0.005). Post hoc tests (step down Holm–Bonferroni procedure) revealed only GFR_{inu}, and GFR_{demo} were significantly different from each other. Performance of the two equations when estimating GFR_{inu} in the normal, extreme and over-hydrated body composition groups is shown in Table 1 and Figures 4 and 5. An apparent dependency in GFR estimation error on absolute GFR was present using both estimation methods. However, correlations between estimated (GFR_{BIA}) and actual GFR (GFR_{inu}) were stronger, SEE was lower, bias was reduced and both limits of agreement and accuracy were improved when including muscle mass (ALM_{BIA}). If actual MDRD generated constants were used rather than constants as generated on this data set, GFR_{demo} performance was substantially worse (data not shown).

Discussion

A quick, cheap and clinically obtainable marker of muscle mass would be very beneficial for management of patients with CKD. In the current study, we tested the validity of a published equation using bioelectrical impedance to predict ALM [12], a validated proxy measure of total body skeletal muscle mass [13]. Unfortunately, performance of this equation was poor in our CKD patients, showing large bias, relatively low correlation, large SEE and a significantly overestimated predicted muscle mass. Of course, methodological differences between our studies may account for some of this bias, but it is highly unlikely that methodological differences can completely explain the poor equation performance shown in this CKD population.

In developing their equation, Kyle et al. [12] excluded patients with CKD and fluid abnormalities, so it is not surprising that the error in prediction we found in our CKD patients was due in part to an altered hydration state, as evidenced by positive correlations between bias and hydration of the fat.

Post hoc
Predicting muscle mass and GFR using BIA in CKD

### Table 1. Performance of prediction equations in our data set

<table>
<thead>
<tr>
<th>Equation Type</th>
<th>Mean GFR (ml/min)</th>
<th>Bias (ml/min)</th>
<th>LoA (ml/min)</th>
<th>Mean error (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole data set</td>
<td>GFRdemo</td>
<td>0.714 (24.9)</td>
<td>-10.3</td>
<td>49.0</td>
<td>-8.6</td>
</tr>
<tr>
<td>Normal body composition</td>
<td>GFRBIA</td>
<td>0.853 (18.6)</td>
<td>-3.2</td>
<td>37.7</td>
<td>6.0</td>
</tr>
<tr>
<td>Extreme body composition</td>
<td>GFRdemo</td>
<td>0.720 (18.8)</td>
<td>-6.0</td>
<td>36.2</td>
<td>-9.6</td>
</tr>
<tr>
<td>Over-hydrated patients</td>
<td>GFRBIA</td>
<td>0.743 (18.1)</td>
<td>-2.4</td>
<td>34.7</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Extreme body composition, ALM index or fat mass index > ±1SD of our sample mean; Over-hydrated patients, hydration of the fat free mass > ±2SD of normal values; GFRdemo, prediction equation including demographic variables as used in MDRD equation; GFRBIA, prediction equation including BIA determined ALM; Correlation, Pearson’s correlation coefficient between actual and predicted GFR; SEE, standard error of the estimate; Bias, mean difference between predicted and GFRinu; LoA, limits of agreement, width of the SD of the mean bias x 1.96; Accuracy, percentage of results that did not deviate by more than 30 and 50% of GFRinu.

Our new equation showed similar performance in our CKD sample to that of the original Kyle *et al.* [12] equation in their sample. The amount of variance in ALM explained by the original equation in their transplant patient group was 91%, compared with 92% for our equation in CKD patients, while the internal error in prediction was originally 1.5 kg and was 1.6 kg in our CKD patients. Additionally, we calculated estimated error in external samples (root mean square error) of our equation to be 1.8 kg. To the best of our knowledge this is the first equation to use bioelectrical impedance to predict muscle mass in CKD patients who do not have conditions causing overt, clinically obvious oedema (e.g. congestive heart failure).

The ability to predict muscle mass quickly and accurately means inclusion of muscle mass measures in estimating GFR becomes a possibility. Previous authors have speculated that body composition may be important in GFR prediction [3–5,17], and several studies have demonstrated improved GFR prediction following the inclusion of muscle mass estimations [6,9,18–21]. Sanaka *et al.* [9], studying frail elderly patients, showed that using muscle volume of the thigh determined by computed tomography as a marker of muscle mass provided significantly better prediction of creatinine clearance than the Cockroft and Gault formula [18]. However, computed tomography is not widely available and is associated with high parameters reflect the fat-free mass (height²/resistance) [15] and the body cell mass (reactance) [16]. There are several likely reasons for their preferential selection. First, in CKD patients the influence of demographic/anthropometric variables on muscle mass is likely to be less important due to disease state. Second, in a healthy population as used to generate the Kyle *et al.* [12] equation, differences in weight reflect differences in muscle mass reasonably well; however, this may not be the case in a CKD population affected by factors such as altered hydration status.

free mass in our data set. Due to the evident shortcomings of this published equation in CKD patients, we developed and cross-validated a CKD specific equation using similar principles and predictors as suggested by Kyle *et al.* [12] but with different constants. Interestingly, in contrast to the original equation, stepwise regression selected both bioelectrical impedance parameters suggested by Kyle *et al.* [12] in preference to demographic and anthropometric parameters. The bioelectrical impedance generated...
radiation exposure and significant cost, and thus is not a clinically obtainable means of assessing body composition in CKD patients.

In a series of studies Donadio et al. [19–21] used bioelectrical impedance to estimate body cell mass and in turn used this measure to predict kidney function. Data regarding the validity of the body cell mass prediction in patients with CKD was not provided. Nevertheless, Donadio et al. showed improvements in bias and limits of agreement when using estimated body cell mass as compared with the Cockroft and Gault formula to predict 24 h creatinine clearance [19] and also for predicting GFR by $^{99m}$Tc-DTPA clearance relative to predictions from 24 h urine collections [20] and relative to the MDRD equation [21]. No comparisons with the MDRD method using constants generated on their own data set were made. Finally, Taylor et al. [6] studied 10 subjects and found using total body lean mass by dual energy X-ray absorptiometry improved GFR estimation as compared with the MDRD equation with its original constants.

These previous findings were confirmed and explained by empirical evidence in our companion study where we showed that muscle mass mediates the relationship between predictor demographic/anthropometric variables and serum creatinine estimated GFR$_{\text{inu}}$, and that including a measure of muscle mass explains considerably more of the variance in GFR$_{\text{inu}}$ than demographic/anthropometric variables alone [4]. Taken together, these findings strongly suggest that using muscle mass or body cell mass in GFR equations will improve their performance. In the current study, we provide a cross-validated method for predicting muscle mass that could be used in the clinical setting instead of more expensive and less available techniques such as dual energy X-ray absorptiometry. However, there will be error associated with any indirect method to predict muscle mass, and it is important to know whether GFR estimation is still improved despite this prediction error. In regard to this, our results suggest that when estimating GFR, performance of the equation when including bioelectrical impedance predicted muscle mass was substantially improved, showing reduced bias, and better limits of agreement and accuracy relative to equations including only demographic variables. This was the case whether analysing patients with either normal or extreme body composition, or altered hydration status. As our data set should be representative of a normal CKD population, these findings strongly suggest there is a real clinical benefit in using markers of muscle mass for GFR prediction.

Limitations of this study include our criterion measure of muscle mass being sensitive to hydration status, and that the single-shot total body inulin clearance method employed is associated with some within-patient variability (7.1% over a 3-week period) [22]. Additionally, the method we propose does not completely abolish the apparent dependency of GFR estimation error on absolute GFR that has been noted by other authors [23]. It should also be noted that our sample size is relatively small in comparison to the wide interval of GFR assessed. However, we generated predictive equations for GFR$_{\text{inu}}$ principally to test the hypothesis that including a clinically obtainable measure of muscle mass will improve GFR estimation. While we provide enough information for this method to be used in its present form, this method requires generation from a larger data set (an $n$ of 100 is recommended by KDOQI) before being used in clinical practice. Our sample also contains more males than females, and future studies must address these limitations by increasing sample size and ensuring a more even gender split. Nevertheless, in its present state this equation is, to the best of our knowledge, the only one that is both clinically obtainable and theoretically and empirically valid, and that uses a method that is likely to provide more accurate results, especially in patients with extreme body composition such as the muscle wasted and obese. For example, this method may prove especially useful in the diabetic population who often show poor equation performance due to altered body composition [24]. As diabetics were not recruited in the present study, further validation of GFR estimation using our method to predict muscle mass is now required in this and other specific populations.

In conclusion, we present a valid and clinically obtainable method to predict muscle mass in patients with CKD. This method, which utilizes bioelectrical impedance, may prove to be useful for monitoring the nutritional status of this population. In the accompanying article [4], we presented empirical evidence suggesting that including a measure of muscle mass explained more variance in GFR than anthropometric and demographic variables alone. The present article provides clinically relevant evidence to support this hypothesis, since we demonstrated that including bioelectrical impedance predicted muscle mass substantially improved performance of GFR estimation, especially in patients with extreme body composition. Further development and validation of this method is now required before implementation in clinical practice.

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Conflict of interest statement. None declared.


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