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The Effects of Racial Differences on Body Composition and Total Body Water Measured by Multifrequency Bioelectrical Impedance Analysis Influence Delivered Kt/V Dialysis Dosing

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Key Words
Multifrequency bio-impedance · Dialysis dosing · Extracellular water · Body composition · Muscle fat

Abstract
Introduction: Haemodialysis dosing is traditionally based on urea clearance (Kt/V). Aiming for the same Kt/V target, some racial groups have better survival. We investigated whether body composition differs with ethnicity and may lead to differences in Kt/V delivered. ***Methods:*** We compared total body water (TBW) measured by multifrequency bioelectrical impedance analysis (MF-BIA) that calculated from standard anthropometric equations. ***Results:*** Three hundred and seventy-one adult patients, with a mean age of 58.2 ± 16.6 years, 60.6% of whom were male, 29.1% diabetic, 38.5% Caucasoid, 29.4% African/Afro-Caribbean, 24.8% South Asian and 5.4% East Asian, were studied. TBW measured by MF-BIA differed significantly from that predicted by anthropometric equations. Body fat of women and diabetics was greater, and muscle mass in South Asians was reduced. The difference between the TBW MF-BIA measurement and that of the equation by Watson et al. [11] was associated with % muscle mass (β –10.8, $p < 0.001$), age (β 0.23, $p < 0.001$), serum albumin (β –0.24, $p < 0.001$), body mass index (β 0.91, $p = 0.001$) and racial origin (β –9.86, $p = 0.04$). ***Conclusions:*** Variation in body composition between ethnic groups potentially leads to over-estimation of delivered dose for some ethnic groups and underestimation for others when using anthropometric equations. MF-BIA assessments of body water should be evaluated as a method for dosing dialysis patients.

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Introduction

Although there is debate as to the toxicity of urea [1, 2], the first randomized, controlled trial of haemodialysis dosing, the National Co-Operative Dialysis Study (NCDS) [3], defined an 'adequacy' threshold based on dialyser urea clearance. Whereas endogenous renal function is typically corrected for body surface area, urea clearance was corrected for body water. Urea clearance is expressed as Kt/V, where K is dialyzer urea clearance, t is the duration of the dialysis session and V is the urea volume of distribution. The NCDS study reported that for standard thrice-weekly haemodialysis, complication-free survival was reduced when the sessional Kt/V was <0.9 [4]. Greater patient survival rates were subsequently reported with higher doses [5, 6] and so by consensus, sessional Kt/V

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targets were increased to 1.2 [7]. However, the haemodialysis (HEMO) study did not find that increasing Kt/V further improved survival [8], although secondary analysis suggested that women may benefit from higher Kt/V doses [8]. As men and women typically differ in body composition, this led to speculation that dialysis dosing using anthropometric equations could lead to under-dosing for small women [9, 10]. In healthy patients, there is a strong correlation between these anthropometric equations [11, 12] and total body water (TBW) measured by bio-impedance techniques [13]. However, body composition not only varies between sexes but also with chronic disease and other factors [14–17]. We therefore decided to compare TBW estimation by standard anthropometric equations and bio-impedance in an ethnically diverse haemodialysis population.

Methods and Patients

Three hundred and seventy-one established haemodialysis outpatients attending for their mid-week dialysis session were audited. Patient ethnicity was taken from NHS records, patients were categorized as Caucasoid, South Saharan African or Afro-Caribbean, South Asian (India, Bangladesh and Pakistan), or Eastern Asian (China, Thailand and the Philippines) or other racial groups (typically North African), with cases of mixed racial origin being excluded.

Multifrequency bioelectrical impedance analysis (MF-BIA) measurements were made after dialysis (InBody 720 Body Composition Analysis, Biospace, Seoul, South Korea) [18], using tetrapolar 8-point tactile electrodes [19]. Patients with cardiac pacemakers, implantable defibrillators, amputees and those unable to stand on the bio-impedance device were excluded. All patients dialysed using Fresenius F4000H or 5000H dialysis machines (Fresenius, Bad Homburg, Germany), polysulfone high flux dialyzers (Nipro Corporation, Osaka, Japan) [20], with ultrapure quality dialysis water and anticoagulated with a low molecular weight heparin (Tinzaparin, Leo Laboratories, Princes Risborough, UK) [21]. Pre- and post-dialysis dialysis blood samples were measured with a standard laboratory auto-analyser (Roche Integra, Roche diagnostics, Lewes, UK) and haemoglobin (XE-2100 Sysmex Corporation, Kobe, Japan).

Body water was calculated using a series of anthropometric equations [11, 12, 15, 22] and previous bio-impedance-derived equations [14, 17] (online suppl. appendix; for all suppl. material, see www.karger.com/doi/10.1159/000355009).

Ethical approval was granted by the local ethical committee as part of the UK NHS Audit and Clinical Service Development.

Statistical Analysis

Results are expressed as mean ± standard deviation, or median and interquartile range or percentage. Statistical analysis was by χ^2 analysis, corrected for small numbers by the Yates correction, the Student t test for parametric data and the Mann-Whitney U test for nonparametric data, with the Bonferroni correction for multiple analyses where appropriate, and by ANOVA with the Tukey post hoc correction. Bland-Altman analysis was used to compare TBW by different equations and MF-BIA. Simple correlation analysis was performed with the Spearman rank correlation and then multiple linear regression analysis using backward-step multivariate analysis was used, excluding variables that were not significant and did not improve the fit of the model and retaining variables where the 95% confidence intervals for the estimate did not include zero or there was an improvement in model fit (as demonstrated by the –2 log likelihood), and with nonparametric variables log-transformed to allow analysis. Statistical analysis used Graph Pad Prism version 6.0 (Graph Pad, San Diego, Calif., USA), Analyse-It (Leeds, UK) and SPSS version 17 (University Chicago, Ill., USA). Statistical significance was taken at or below the 5% level.

Results

We studied 371 adult patients, mean age 58.2 ± 16.6 years, 60.6% male, 29.1% diabetic and dialysis vintage 51 (10–82) months. Ethnic distribution was 38.5% Caucasoid, 29.4% South Saharan African or Afro-Caribbean, 24.8% South Asian, 5.4% East Asian and 1.9% other races, typically North African. Patient weight pre-dialysis was 72.3 ± 16.2 kg and height 165.5 ± 10.4 cm, dialysis session time 3.9 ± 0.05 h with a urea reduction ratio 73.4 ± 7.1%. Pre-dialyis blood results included haemoglobin 114.0 ± 15.0 g/l, albumin 40.9 ± 3.8 g/l, median C-reactive protein 4 (2–11) mg/l and glucose 5.9 (4.8–8.4) mmol/l.

Post-dialysis body mass index (BMI) was 25.8 ± 5.3. TBW, measured by MF-BIA post-dialysis was 35.1 ± 7.5 litres, intracellular water 21.6 ± 4.7 litres and extracellular water (ECW) 13.5 ± 2.8 litres. Skeletal muscle mass was determined at 26.3 ± 6.2 kg, fat mass 22.9 ± 11.9 kg, giving a percentage body skeletal muscle content of 37.6 ± 6.9% and a fat content of 31.4 ± 13%.

TBW measured by MF-BIA differed significantly from that predicted in the equations derived by Watson et al. [11], Hume and Weyers [12], Lee et al. [14], Chumlea et al. [15], Chertow et al. [17] and the HEMO study [22] (fig. 1). Bland-Altman analysis showed that TBW measured by MF-BIA was lower than that estimated by these equations (table 1).

As expected, percentage body fat was greater in women than in men (36.6 ± 10.5 vs. 28.6 ± 13.6%) and correspondingly, skeletal muscle mass was greater in men than in women (39.6 ± 6.6 vs. 34.2 ± 6.0%), $p < 0.05$ (online suppl. table 1). Similarly, percentage body fat was greater in diabetic patients compared to non-diabetics (36.1 ± 10.1 vs. 29.6 ± 13.6%) and correspondingly, skeletal muscle mass was greater in non-diabetics than in diabetics (38.9 ±

Table 1. Comparison of TBW in 371 haemodialysis patients measured by anthropometric equations and by standard MF-BIA

	Watson et al. [11]	Hume and Weyers [12]	Chumlea et al. [15]	HEMO study [22]	Chertow et al. [17]	Lee et al. [14]
Correlation	0.12	0.02	0.12	0.44	0.06	0.23
Bias	1.45	2.18	2.66	–4.77	4.74	1.33
95% CL	1.03–1.87	1.78–2.59	2.24–3.09	–5.4 to –4.3	4.34–5.15	0.91–1.74
t Statistic	6.74	10.67	12.36	–21.07	23	6.21
SD	4.13	3.94	4.15	4.35	3.97	4.11
95% LA	–6.66 to 9.55	–5.54 to 9.9	–5.47 to 10.8	–13.29 to 3.76	–3.04 to 12.53	–6.7 to 9.38

Bland-Altman correlation of absolute difference versus average (Correl), bias and 95% confidence limits (95% CL), t statistic, standard difference (SD) and 95% limits of agreement (95% LA). $p < 0.0001$.

Table 2. Comparison of TBW measurements (in litres) amongst patients from different ethnic backgrounds taken from anthropometric equations, MF-BIA and MF-BIA-derived body composition

	Caucasoid	African[a]	South Asian	East Asian	Other
Number of patients	143	110	92	20	7
BMI	26.3±5.3	25.9±5.6	25.1±4.9	23.7±3.7	25.7±5.6
Watson et al. [11]	37.3±6.9	37.3±6.6	32.4±7.2	33.6±8.2	37.3±4.7
Hume and Weyers [12]	38.4±6.9	38.1±6.3	35.6±7.7	33.5±7.9#	36.8±4.9
Chumlea et al. [15]	38.8±7.4	38.3±7.3	36.4±7.9	34.5±8.4	40.1±7.5
HEMO study [22]	30.3±5.8	32.0±5.7	29.1±6.4	27.7±7.1#	30.6±4.0
Chertow et al. [17]	40.9±7.7	32.0±5.7	29.1±6.4#	36.0±8.4	39.4±5.3
Lee et al. [14]	37.6±7.4*	37.4±6.9	34.7±8.0	32.3±8.3	35.9±5.1
MF-BIS	36.2±7.5*	36.8±7.1	32.4±7.2	32.1±7.8	34.0±3.8
ICW	22.2±4.7*	22.8±4.6*	19.8±4.5	19.9±5.1	21.2±2.4
ECW	14.0±2.8*	14.0±2.6*	12.5±2.8	12.2±2.8	12.8±1.5
% SMM	37.4±6.3	39.0±7.4*	36.0±6.9	39.4±7.1	35.7±5.6
% Fat	31.2±10.6	30.6±17.0	33.4±7.9	25.9±8.1	35.5±9.5

Values expressed as mean ± SD or percentage. After Bonferroni correction for multiple analyses, * $p < 0.05$ versus South Asian and # $p < 0.05$ versus African/Afro-Caribbean. SMM = Skeletal muscle mass.

[a] African/Afro-Caribbean.

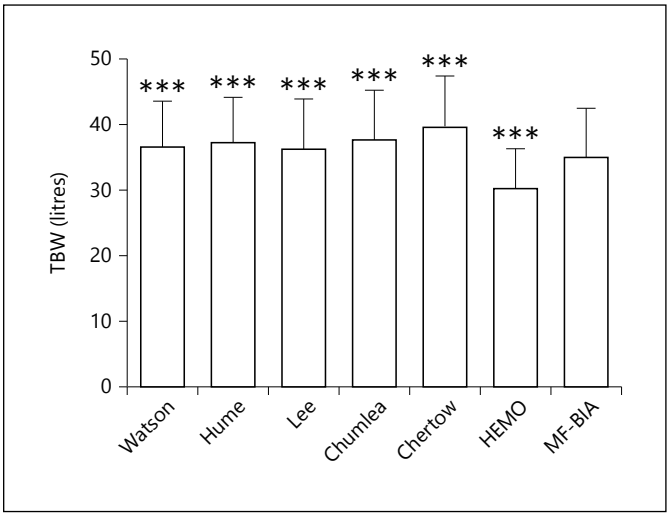

Fig. 1. TBW calculated by anthropometric equations and measured by MF-BIA. *** $p < 0.001$ versus MF-BIA. Equations are displayed in the supplementary appendix.

7.0 vs 34.3 ± 5.4%), $p < 0.05$ (online suppl. table 1). There was no difference in the proportion of male and female diabetic patients ($\chi^2 = 0.79$, $p = 0.41$). Compared to the other major ethnic groups, those from the South Asian subcontinent had a greater percentage of body fat and less muscle, despite a similar BMI (table 2). The ratio of ECW/TBW post-dialysis was significantly lower in the African/Afro-Caribbean than in both Caucasoids and South Asians, 0.38 ± 0.1 versus 0.39 ± 0.1, $p < 0.05$. There was no difference in sex distribution between the ethnic groups ($\chi^2 = 6.15$, $p = 0.188$); however, relatively more South Asians were diabetic (40.2%) when compared to the Caucasoid (28.7%), African/Afro-Caribbean (24.8%) and East Asian (10%) patients ($\chi^2 = 12.96$, $p = 0.011$). As such, body

Table 3. Multiple linear regression backward-step analysis of factors associated with the percentage difference between TBW measured by MF-BIA and by the equation by Watson et al. [11]

Variable	F	β	SE	t	95% CL	p value
Age, years	172.1	0.226	0.017	13.1	0.19 to 0.26	<0.0001
Albumin, g/l	11.5	–0.238	0.07	–3.39	–0.38 to –0.10	<0.0001
BMI, kg/m^2	184.1	0.913	0.067	13.57	0.78 to 1.05	0.001
% SMM	1,531.4	2.40	0.06	39.13	2.28 to 2.52	<0.0001
DM	3.35	–10.79	4.32	–2.50	–19.6 to –2.28	0.068
Race	2.54	–9.86	4.94	–1.99	–19.5 to –0.15	0.04
Sex, male	185.4	10.46	4.43	2.36	1.8 to 19.2	<0.0001
DM + race	1.8	11.51	4.46	2.58	2.74 to 20.28	0.147
DM + sex	5.29	4.85	2.16	2.25	0.61 to 9.09	0.022
Race + sex	5.14	–10.5	4.56	–2.31	–19.4 to –1.57	<0.0001
Race/sex/DM	1.47	–1.8	2.95	0.61	–7.6 to 4.0	0.23

Final r2 value for model 0.876 (corrected r2 = 0.868). CL = Confidence limits; DM = diabetes mellitus; SE = standard error; SMM = skeletal muscle mass.

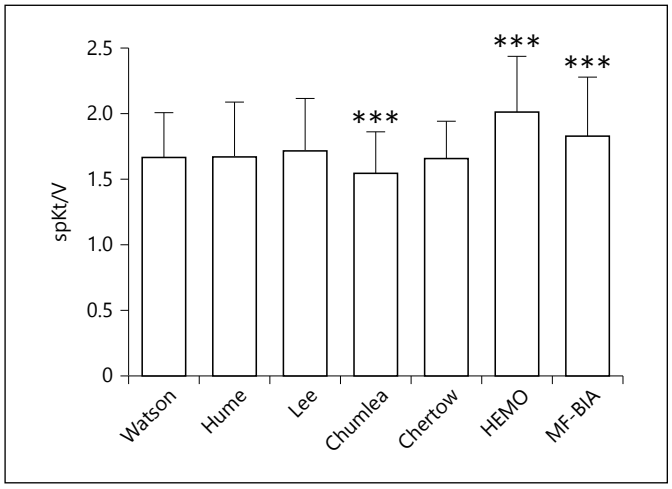

Fig. 2. Rescaled delivered Kt/V in South Asians, using TBW calculated by anthropometric equations and that measured by MF-BIA. *** $p < 0.001$ versus the equation by Watson et al. [11]. Equations are displayed in the supplementary appendix.

composition differed not only between sexes and according to diabetic status, but also between ethnic groups.

South Asians typically had more fat and less muscle than the Caucasoid and Afro-Caribbean groups, and so had a relatively lower TBW, adjusting single-pool sessional Kt/V for the volume of urea distribution. Delivered Kt/V was greater using MF-BIA and the HEMO equation compared to the equation by Watson et al. [11] and lower when TBW was estimated by the equation by Chumlea et al. [15] (fig. 2).

To investigate the difference between TBW measured by MF-BIA and that calculated by the equation of Watson et al. [11], the simple Spearman correlation analysis was performed and there was an association for age, sex, diabetes, weight, height, BMI, urea reduction ratio, post-dialysis blood pressure, haemoglobin and both skeletal muscle mass and body fat (online suppl. table 2). A multiple step-wise regression model was then constructed, using the factors in table 3 and other variables with a p value of <0.1, including albumin and C-reactive protein. Variables were then subsequently eliminated, if they were not significant or did not improve the model fit. Age, pre-dialysis serum albumin, BMI, percentage skeletal muscle mass, diabetic status, sex and ethnicity remained significant in the statistical model (table 3).

Discussion

The NCDS study helped define a lower limit for dialysis dosing, based on urea clearance [3, 4], but subsequent prospective studies failed to show that simply increasing dialysis Kt/V improves patient survival [8]. Previous studies from the USA reported greater mortality for Caucasoid patients, particularly women, than for African-Americans [23], whereas women in the general population outsurvive men. On the other hand, there appears to be a survival advantage for the morbidly obese (BMI >35) haemodialysis patient whereas in the general population, the morbidly obese have increased mortality. Kt/V-based dosing for haemodialysis could potentially lead to a

shortening of dialysis session times for women but to extended times for the morbidly obese, potentially impacting on both phosphate and middle molecule clearances [24], but also on volume control and sodium balance [25].

The newer generation of haemodialysis machines is equipped with on-line clearance measurements that assess delivered Kt/V. However, the algorithms used by these devices typically rely on V which has been derived from anthropometric equations. In the UK, the size and body composition of the general population has changed since records were kept after the Second World War, with the general population increasing in both height and weight over time. The standard equation for calculating TBW used by Watson et al. [11], which is recommended by many clinical guideline committees, was derived from a series of earlier studies of around 700 adults from the 1950s and 1960s. For the studies where height was not available, this was recalculated using body surface equations derived from reports dating back to around the First World War [26]. Although it is well recognized that muscle and fat mass change with age, it is also clear that body composition is affected by obesity [27] and other co-morbidities, including diabetes [28]. In addition, body composition differs between ethnic groups [29]. The estimates of TBW varied with the different anthropometric equations, and this probably reflects differences in the composition of the original study cohorts, for example, the equation by Chumlea et al. [15] was derived from a Caucasoid population with no ethnic minorities [15], and it is generally recognized that African-Americans have greater bone mineral density and body protein than Caucasoids [30], in keeping with the lower ECW/TBW measured with MF-BIA. We measured TBW using MF-BIA equipment validated in healthy controls, the obese [31] and dialysis cohorts [16, 32]. TBW calculated using anthropometric equations was generally overestimated TBW when measured by MF-BIA, in keeping with an earlier report using single-frequency bio-impedance [33]. The HEMO equation [22], which was a modification of the equation by Watson et al. [11], had the greatest correlation with MF-BIA, but had a significant negative bias. Our patient cohort differed from the HEMO study patients, not only in terms of ethnicity, but also patient size, as the HEMO study only recruited patients who could achieve a target Kt/V within a relatively short dialysis session. As such, the very obese were excluded from the HEMO study. The HEMO study equation may have also overestimated the effects of changes that occur in the diameter of the dialysis blood lines at high blood-flow rates and during shorter high-efficiency dialysis treatments, the apparent urea distribution volume may be somewhat less than TBW [34]. In addition, our MF-BIA-measured TBW was less than that predicted from two equations derived from previous bio-impedance estimations. However, the equation by Chertow et al. [17] was based on a single-frequency bio-impedance that was measured predialysis, when patients were volume-overloaded and similarly, the equation by Lee et al. [14] used an earlier bio-impedance device with a reduced spectral frequency range, and the accuracy of bio-impedance for body composition measurements increases with the spectrum of electrical frequencies used [35].

Patients with chronic kidney disease may suffer from protein energy wasting which will alter body composition and body water content. As such, when using TBW to dose haemodialysis by Kt/V, then overestimation of TBW for any given predicted Kt/V will result in an increased delivered dose of dialysis whereas underestimation of TBW for the predicted same Kt/V will reduce this dose. In our study, the average difference between measured TBW with MF-BIA and that calculated from the equation of Watson et al. [11] was greater for men than for women, for diabetics compared to non-diabetics, and for South Asians compared to African/Afro-Caribbean subjects. The greatest differences between measured TBW by MF-BIA and that estimated by anthropometric equations occurred in patients with similar BMI, but with more fat and reduced muscle mass. This may help to explain the apparent paradox of increased survival for the very obese haemodialysis patients in North America compared to those with a normal BMI [36], as the patients have proportionately much more fat and so to achieve an adequate Kt/V based on anthropometric equations, they require more prolonged dialysis sessions, potentially increasing sodium and middle molecular weight clearances [37]. On the other hand, underdosing of various groups could also occur, because on multiple regression analysis, the difference between measured and calculated TBW was affected by pre-dialysis serum albumin, BMI and percentage skeletal muscle mass as well as diabetic status, sex and ethnicity. The body composition of Caucasoids and African/Afro-Caribbean subjects was different, particularly for women. This may help explain, to some extent, some of the differences in mortality previously reported between different ethnic groups and sexes [23], as female Caucasoids are more likely to receive lower dialysis doses than Africans/Afro-Caribbean subjects. In addition to ethnic differences, we also noted changes with diabetes, again leading to increased body fat and loss of muscle mass.

This was most apparent in our South Asian population, who tended to have a lower muscle mass than Caucasoids and Africans/Afro-Caribbean subjects.

An alternative approach to try and prevent underdosing of haemodialysis patients has been to rescale Kt/V according to body surface area [22]. When the dose of dialysis in the HEMO study was normalized to body surface area rather than TBW, then the dose of dialysis delivered to women was found to be substantially lower than that for men [22]. As the lowest surface-area-normalized dose was delivered to those women randomized to the lower or conventional dose arm, this could possibly explain the difference in dialysis dose and survival in the women reported [8]. More recently, there have been reports of surface-area-based dialysis dosing resulting in mortality rates that are substantially different from those with volume-based dosing, again suggesting that repetitive underdosing of women due to volume-based Kt/V prescription leads to increased patient mortality [37].

Our data show that the differences between calculated and measured body water are not only related to body surface area, but are also affected by body composition. As changes in skeletal muscle and fat mass vary with age, ethnicity and also diabetes, body composition can be significantly different between individuals despite a similar BMI or body surface area. Thus, further studies, using MF-BIA to measure body composition and TBW are required to determine how best to prescribe dialysis so that all patients indeed receive an adequate dose.

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