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The Body Composition Monitor: a flexible tool for routine fluid management across the haemodialysis population

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Abstract

Bioimpedance measurements with the Body Composition Monitor (BCM) have been shown to improve fluid management in haemodialysis. However, there is a lack of a sufficiently robust evidence-base for use of the BCM outside of standard protocols. This study aims to define the error associated with BCM measurement using alternate paths and timings to allow the use of BCM with confidence in a range of clinical scenarios. BCM measurements were made in 48 healthy controls and in 48 stable haemodialysis patients before and immediately after dialysis. The effect of utilising alternative measurement paths was assessed using mixed effects models and the effect of measuring post-dialysis was assessed by comparing changes in BCM-measured overhydration (OH) with weight changes over dialysis. The data from healthy controls suggest that there is no difference in BCM-measured OH between all the whole-body paths other than the ankle-to-ankle measurement. Dialysis patients showed similar results other than having higher BCM-measured OH when measured across the site of a vascular access. There was good agreement between BCM-measured OH from the standard path and change in weight, suggesting post-dialysis measurements can be utilised. These results suggest BCM protocols can be flexible regarding measurement paths and timing of measurement to ensure as many patients as possible can benefit from the technology.

Introduction

Fluid management is an important part of care for haemodialysis patients (Wizemann et al., 2009). There is growing evidence that the use of bioimpedance measurements with the body composition monitor (BCM; Fresenius Medical Care, Germany) can help guide fluid management and improve outcomes (Moissl et al., 2013, Onofriescu et al., 2014). However, there are few pragmatic studies that can help to inform the use of BCM outside of the strict protocol recommended for measurements and used in interventional studies, which can exclude a significant number of patients when BCM is used as part of routine care.

Manufacturer's guidance state that measurements should be made before dialysis with the patient in a supine position (Fresenius Medical Care, 2009). This is related to the effect that ultrafiltration (Abbas et al., 2014) and posture (Zhu et al., 1998) have on fluid distributions between body segments and that, due to the different shapes and sizes of the limbs, shifts in fluid between segments can have significant effects on the whole body impedance. Measurements should also be made from wrist-to-ankle – as this is the only validated measurement path – and should avoid peripheral access sites, due to the presence of anatomical changes. As such, the standard path that is supported by the BCM manufacturer is from wrist-to-ankle on the opposite side of the body to the patient's vascular access.

However, in practice these requirements would exclude a relatively large number of patients from having BCM measurements. The haemodialysis population is highly comorbid and is disproportionately prone to amputations and tissue viability problems. Heavily bandaged limbs, damaged skin and amputations can prevent the use of the standard measurement path, while some complications may not prevent a measurement but will significantly affect the quality of the measurement – e.g. use of moisturisers, localised fluid accumulations or contact between body segments such as at the armpit or between the legs. Validated alternative paths would allow measurements to be made on patients who would otherwise have been managed without BCM or managed based on poor quality data. There are also a number of situations where it would be helpful to make post-dialysis BCM measurements. Practicalities and staffing levels can sometimes make it difficult to carry out all necessary BCM measurements at the same time as putting patients on dialysis, while post-dialysis measurements also allow immediate action to be taken when intradialytic symptoms prompt a review of target weights.

The potential for the equivalence of impedance across different paths was demonstrated two decades ago using consecutive bioimpedance analysis (BIA) measurements on the right and left sides of the body (Lukaski et al., 1985) – although the approach to analysis in BIA differs considerably to that of bioimpedance spectroscopy (BIS) (Kyle et al., 2004), employed by the BCM. The only investigation to consider alternative paths with BIS measurements was in preliminary work for this study, where it was shown that BCM-measured overhydration (OH) from the wrist-to-wrist path is an acceptable alternative to the standard

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2
3 path (Keane and Lindley, 2015). When considering post-dialysis measurements, it is
4 accepted that haemodialysis induced changes in fluid distributions affect whole-body
5 bioimpedance (Zhu et al., 1999), but the clinical significance of this when using BCM needs
6 clarification.
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10 In order to allow greater understanding of the effect of making measurements outside the
11 manufacturer's protocol on body composition parameters, this study aimed to characterise
12 the error associated with alternate measurements that could be clinical useful.
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16 17 **Methods**

18 19 *Subjects*

20 Ethical approval was granted by a local ethics committee and all participants provided
21 informed consent.
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25 A cohort of healthy controls was recruited (n=48), stratified by age-decade and by sex, who
26 had no history of kidney disease or heart failure, no visible fluid accumulations and no limb
27 amputations. Additionally, a cohort of stable haemodialysis patients was recruited (n=48),
28 being over 18 years old, having no visible localised fluid accumulations and achieving target
29 weight. Haemodialysis prescriptions were for regimes of three sessions of four hours per
30 week, dialysate temperature was 36°C and sodium was 137mmol/l as standard. Routine
31 target weights were defined on the basis of clinical examination and BCM on indication.
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36 37 *Sample size*

38 Pilot work comparing BCM measurements from wrist-to-wrist and from wrist-to-ankle
39 showed standard deviations of the mean difference in OH of around 1.0 litres (Keane and
40 Lindley, 2015). Recruiting 48 subjects into each cohort would allow differences of 0.3 litres
41 to be measured between the primary two paths at the level of 5% type I error with 80%
42 power using a two sided t-test. This is deemed an acceptable sample size; differences below
43 0.3 litres will fall below the limits of reproducibility of the device (Wieskotten et al., 2013).
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48 49 *Data collection*

50 Healthy controls had height measured using a stadiometer and weight measured using
51 calibrated scales. For haemodialysis patients, height was taken from their clinical notes and
52 pre- and post-dialysis weights were obtained as part of normal care.
53
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55 BCM measurements were made with the commercially available 4-electrode BCM on the
56 standard path. For this, the impedance is measured between an electrode positioned on the
57 wrist and an electrode on the ankle, while a small electric current is passed between two
58 further electrodes positioned 10 cm distal to the measurement electrodes. Additionally,
59
60

measurements were made with a modified BCM - the 8-electrode BCM - which had additional cables allowing leads to be connected to electrodes on both hands and both feet. This device automatically makes 17 consecutive BIS measurements, varying the electrodes used for the voltage and current paths as described in figure 1. This allows measurement of impedances of the six whole body paths (figure 1, # 1-6), where the current and measurement electrodes define the same path through the body, as well as the impedances of individual segments (figure 1, # 11-16) (Gibson et al., 2008), where the measurement electrodes define a region of the body that is different from the path of the current, thereby isolating particular regions for measurement of segmental impedances. 4- and 8-electrode BCM measurements were made on healthy subjects on one occasion while dialysis patients had measurements made pre- and post-dialysis. All 4-lead BCM measurements were checked visually for artefacts, and repeated until the difference in measured OH was no greater than 0.2 litres between readings (in almost all cases the discrepancy between the first and second readings was no more than 0.1 litre). The 8-electrode device does not display Cole-plots or body composition data to allow real-time assessment of artefacts or consistency, so repeat measurements were not made. Measurements of resistance, reactance and phase angle were made at the same 50 frequencies as in the standard BCM, for seventeen combinations of voltage and current (see fig. 1) and data was extracted for analysis.

#	Voltage	Current	Segments measured
1	RH-RF	RH-RF	Right arm, right trunk, right leg
2	LH-LF	LH-LF	Left arm, left trunk, left leg
3	RH-LF	RH-LF	Right arm, R-L trunk, left leg
4	LH-RF	LH-RF	Left arm, L-R trunk, right leg
5	RH-LH	RH-LH	Right arm, top trunk, left arm
6	RF-LF	RF-LF	Right leg, low trunk, left leg
7	RH-LF	RH-RF	Right arm, right trunk
8	LH-RF	LH-LF	Left arm, left trunk
9	LH-RF	RH-RF	Right leg, right trunk
10	RH-LF	LH-LF	Left leg, left trunk
11	RH-RF	RH-LH	Right arm
12	LH-LF	RH-LH	Left arm
13	RH-RF	RF-LF	Right leg
14	LH-LF	RF-LF	Left leg
15	LH-LF	RH-RF	Right trunk
16	RH-RF	LH-LF	Left trunk
17	RH-RF LH-LF	RH-RF LH-LF	Full whole body

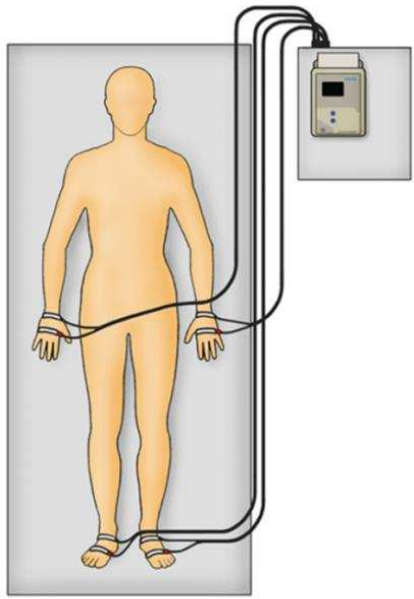


Figure 1: Specifications of an 8-electrode BCM measurement. RH, RF, LH, LF refer to right hand, right foot, left hand and left foot respectively.

8-electrode BCM data processing

Programmes were written in Matlab (v. 2014a; Mathworks In, MA, USA) to process 8-electrode BCM data. For each of the 17 measurements, the data was fitted to the Cole equation as described by De Lorenzo et al. (De Lorenzo et al., 1997) giving the extracellular fluid (ECF) resistance (R_E) and intracellular fluid (ICF) resistance (R_I). The main objectives were focussed on body composition parameters which can only be found from the whole body measurements (measurements 1-6) using volume and body composition models (Moissl et al., 2006, Chamney et al., 2007) for each individual path using optimised tissue hydration parameters (courtesy of Fresenius Medical Care R&D). This provided equivalent data to the standard 4-lead BCM device, which was validated by processing 4-lead BCM impedance data with the custom analysis programme and comparing the results with those calculated by the device (see appendix 1).

Mixed-effects regression model

The use of mixed-effects regression allowed a model to be built that could account for the repeated measures on an individual from the 8-electrode BCM. This characterises the individual differences in fluid status and body composition and accounts for this when describing the differences between the paths at the cohort level.

A different mixed effects model was used to analyse each of the principal BCM parameters - OH, lean tissue mass (LTM) and adipose tissue mass (ATM) - and the models only included measurements of the 6 whole-body paths: right side; left side; right wrist-to-left ankle (cross 1); left wrist-to-right ankle (cross 2); wrist-to-wrist; and ankle-to-ankle. For healthy controls, subject was taken as the random effect and path, sex and age were taken as fixed effects. For haemodialysis patients, the same model set up was used, only with the addition of measurement time (pre- or post-dialysis), which was added as a simple predictor variable for the models of LTM and ATM and as an interaction term for the model of OH, to allow assessment of ultrafiltration associated changes in fluid distributions between the paths.

To present the data, results for a 60 year old female measured on the standard path acted as a reference (standard path was taken as wrist-to-ankle on the dominant side of the body for controls and on and the contralateral side of the body to the most recently used vascular access (VA) for dialysis patients). The mean value for the dependent variable measured on the standard path is presented separately for controls and pre- and post-dialysis for patients, with a 95% confidence interval and a p-value assessing against a null value of zero. For each of the other measurement paths, the difference compared to the reference path is detailed with 95% confidence interval and a p-value. Adjustments for age and sex in each model are given and also for measurement time in the models assessing LTM and ATM. Significance levels were set at 0.05.

To examine each model, plots of standardised residuals against fitted values were used to check the assumption of homoscedasticity and a Q-Q plot of the residuals was used to assess normality.

Statistical analysis

To investigate the validity of post-dialysis measurements, the agreement between change in BCM-measured OH from the reference path and change in weight was assessed using Bland-Altman analysis. Furthermore, the consistency of LTM and ATM from the start to end of dialysis was assessed based on the effect of measurement time in each of the mixed-effects models.

The estimate of R_E from the curve-fitting routine was used as a marker of relative changes in fluid status during dialysis for comparisons between the five body segments (right arm, left arm, trunk, right leg and left leg), where the whole-body analysis models are not appropriate.

Bland Altman analysis was done using Analyse-it for Microsoft Excel (version 2.26). All other analysis was done using the statistical software package 'R' version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

	Healthy controls n=48	HD patients n=48
Age (years)	49 (17)	60 (16)
Height (m)	1.71 (0.11)	1.70 (0.12)
Weight (kg)	73 (14)	81 (23)
BMI (kg/m ²)	25 (4)	29 (7)
Sex (males)	24 (50%)	28 (58%)
HD vintage (months)	-	30 (6)
Most recent VA (left sided)	-	38 (79%)
Albumin (g/L)	-	38 (2.8)
Diabetes	-	14 (29%)
Number of comorbidities - 1	-	12 (25%)
- 2	-	4 (8%)
- 3	-	3 (6%)

Table 1: Subject demographics. Data are mean (standard deviation) for normal data and number (%) of subjects for categorical data. Comorbidities present included acute coronary syndrome, heart failure, cerebrovascular disease, liver disease, peripheral vascular disease and smoking.

Model results

Patient characteristics can be seen in table 1. Details of model checking can be seen in Appendix 2.

The results from the mixed effects regression models for OH can be seen in tables 2 and 3 with the results for LTM and ATM in Appendix 3. For the models investigating OH and ATM, age and sex were not associated with OH, while both age and sex were associated with LTM in both healthy controls and haemodialysis patients. For the model of OH in dialysis patients, including measurement time as an interaction term made a significant difference compared to a model with measurement time as a simple predictor variable ($p=0.02$), indicating the effect of measurement time on OH is modulated by path. For the models of LTM and ATM, including measurement time as an interaction term did not make a difference to the model, suggesting that the effect of measurement time on LTM and ATM was not different between the paths. For these models, measurement time was included as a predictor variable to investigate the validity of post-dialysis measurements of LTM and ATM.

	Measurement Path	OH (litres)	Difference (litres)	p-value	Approx. 95% CI
Healthy controls	Dominant	-0.12	-	0.74	-0.86 to 0.61
	Non-dominant	-	0.09	0.24	-0.06 to 0.25
	Cross1	-	0.002	0.98	-0.15 to 0.16
	Cross2	-	0.10	0.20	-0.05 to 0.26
	Arms	-	-0.02	0.81	-0.17 to 0.14
	Legs	-	0.80	<0.01	0.64 to 0.95

Table 2: Model for OH in healthy controls. Data are presented for a 60 year old female, where the adjustment for OH with age was -0.003 per year ($p=0.65$; 95% CI: -0.02 to 0.01) and with sex was 0.28 for male ($p=0.22$; 95% CI: -0.17 to 0.74). Difference is relative to the dominant path.

	Measurement Path	OH (litres)	Difference (litres)	p-value	Approx. 95% CI
Pre-dialysis	Non-VA side	1.7	-	<0.01	0.66 to 2.7
	VA-side	-	0.42	0.02	0.08 to 0.76
	Cross1	-	0.02	0.91	-0.32 to 0.36
	Cross2	-	0.41	0.02	0.07 to 0.75
	Arms	-	-0.21	0.23	-0.55 to 0.13
	Legs	-	1.7	<0.01	1.4 to 2.1
Post-dialysis	Non-VA side	-0.12	-	0.82	-1.2 to 0.90
	VA-side	-	0.13	0.61	-0.36 to 0.61
	Cross1	-	0.02	0.93	-0.46 to 0.50
	Cross2	-	0.10	0.68	-0.38 to 0.59

Arms	-	0.35	0.16	-0.13 to 0.84
Legs	-	-0.56	0.03	-1.0 to -0.07

Table 3: Model for OH in dialysis patients. Data are presented for a 60 year old female, where the adjustment for OH with age was 0.012 per year ($p=0.38$; 95% CI: -0.02 to 0.04) and with sex was 0.001 for male ($p=0.99$; 95% CI: -0.88 to 0.89). Difference is relative to the non-VA side.

Use of alternate paths

The data from healthy controls show that there is no difference in BCM-measured OH between all the whole-body paths other than the ankle-to-ankle measurement, which had a difference of 0.8 litres (table 2). Considering LTM and ATM, there was a significant difference between the reference path and most other paths, apart from the cross measurements, including higher LTM and lower ATM in the dominant arm and in the wrist-to-wrist path as compared to the reference path.

Haemodialysis patients showed different pre-dialysis patterns than subjects with normal renal function. In particular, there was a significant difference in pre-dialysis BCM-measured OH between the side of the body where vascular access was situated as compared to the contralateral side (0.4 litres; 95% CI: 0.08 to 0.76; table 3), although this effect was not present post-dialysis. Unlike controls, there was no difference in LTM or ATM between the sides (Appendix 3), despite the fact that vascular access is usually on the non-dominant side.

Using the 8-electrode BCM, the impedances of each limb individually can be isolated (figure 1), which can support the results of the regression models. The relative magnitudes of R_E and R_I in each limb expressed in relation to the corresponding value from the reference path (whole body measurement on dominant/non-VA side) can be seen in table 4. Estimation of R_I has much greater uncertainty and for segmental measurements, especially, in the trunk, the data were largely uninformative.

Segment	Control		Pre-dialysis		Post-dialysis		p-value	
	R_E	R_I	R_E	R_I	R_E	R_I	R_E	R_I
Arm_ref (%)	52	56	50	55	48	54	0.02	0.6
Arm_opp (%)	52	59	52	51	50	53	0.06	<0.01
Leg_ref (%)	44	47	44	51	45	50	0.4	0.4
Leg_opp (%)	44	48	43	55	45	52	0.5	0.3
Trunk_ref (%)	4.0	1.4	4.3	1.6	4.1	1.3	0.2	0.3
Trunk_opp (%)	4.0	1.3	4.0	1.5	3.8	1.6	0.3	0.6
Trunk upper (%)	0.2	-	0.3	-	0.1	-	0.8	-
Trunk lower (%)	0.01	-	0.03	-	0.03	-	0.8	-
Trunk_ref-opp (%)	4.0	-	4.1	-	3.8	-	0.3	-
Trunk_opp-ref (%)	4.0	-	4.1	-	3.8	-	0.3	-

Table 4: Relative segmental resistances as a proportion of standard whole body path resistances. Between group differences for R_E and R_I were assessed using one-way ANOVA. 'Ref' indicates a segment from the reference path, 'opp' from the opposite side and ref-opp/opp-ref come from cross measurements.

Use of post-dialysis measurements

There was good agreement between change in BCM-measured OH on the reference measurement path ([pre-dialysis OH] – [post-dialysis OH]) with change in weight (fig. 2; bias 0.3 kg, 95% CI -1.9 to 1.3 kg). In theory, LTM and ATM should not change over dialysis and although there was no significant change in LTM (-0.40 kg; $p=0.1$; 95% CI:-1.1 to 0.1; table A3) there was a difference observed for ATM (0.77 kg; $p=0.01$; 95% CI: 0.16 to 1.4; table A4).

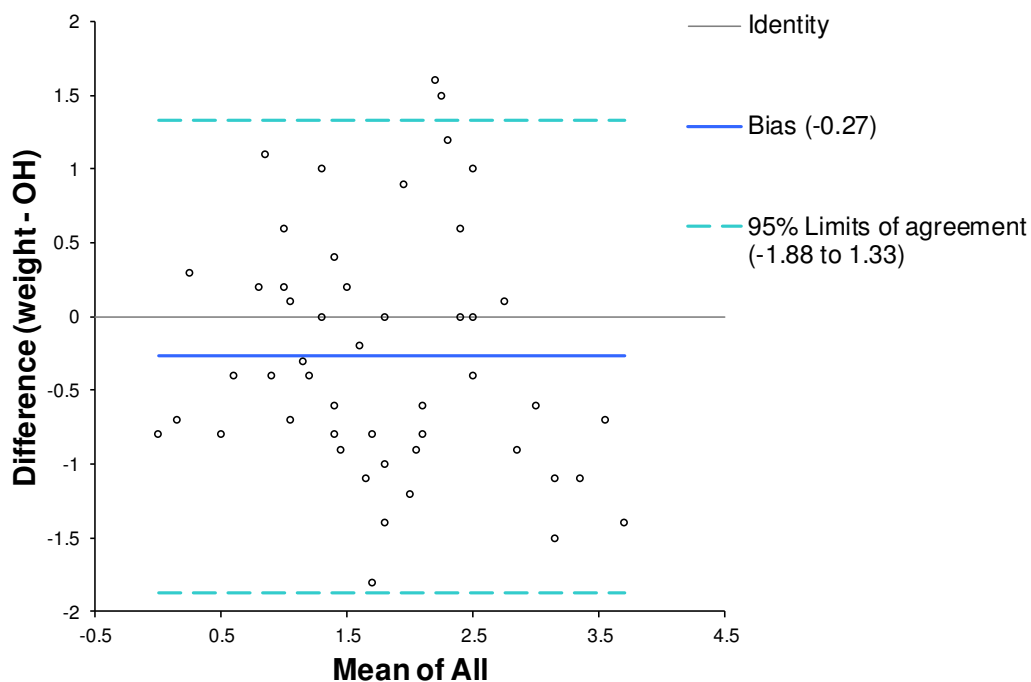


Figure 2: Bland Altman analysis of the agreement of change in weight and change in OH

The use of measurement time as an interaction term in the models for dialysis patients showed that measured-OH changed by a different amount between the paths. The only statistically significant interaction was for the ankle-to-ankle path, which suggests that there is a greater change in BCM-measured OH across this path compared to the other paths. This is supported by looking at the segmental impedance data. If relative changes in R_E over dialysis are used to indicate changes in fluid status, it can be seen that the greatest relative change is in the leg segments (table 5).

Segment	Mean pre R_E (ohms)	Mean post R_E (Ohms)	Mean % change in R_E (Ohms)
Arm_ref	288 (68)	326 (69)	13 (9)

Arm_opp	283 (71)	316 (73)	12 (8)
Trunk	23 (7)	25 (5)	6 (7)
Leg_ref	248 (63)	295 (73)	19 (8)
Leg_opp	247 (63)	294 (73)	19 (7)

Table 5: Segmental changes in ECF resistance (R_E) over dialysis with a mean ultrafiltration volume of 1.9 litres. 'Ref' indicates a segment from the reference path and 'opp' from the opposite side.

Discussion

Rationale for the need for flexible measurement protocols

At a population level, it is becoming well accepted that using BCM as an aide in guiding fluid management in haemodialysis improves outcomes (Onofriescu et al., 2014, Moissl et al., 2013). In an uncomplicated individual with relatively common characteristics, standard measurement protocols - from wrist-to-ankle on one side of the body avoiding vascular access sites - and decision making algorithms are likely to be beneficial. Yet there is a lack of data to support use of BCM outside this standardised approach and there remains a great deal of uncertainty in utilisation of the technology in certain individuals. By making 8-electrode BCM measurements on healthy controls and dialysis patients, the effect of making a number of simple alterations to BCM measurements are characterised which will allow these measurements to be made with greater confidence.

Use of alternate paths

Measurements on healthy controls suggest there is no significant difference in OH from any whole-body path other than across the legs. In principle the models that were generated and validated for the standard path can be employed with alternate paths. Changing from a standard wrist-to-ankle measurement on one side of the body to a wrist-to-wrist or cross measurement will involve substitution of one limb for another and a change in the pathway through the trunk. Using the segmental resistances from dialysis patients in table 4, the different path resistances can be built from the segments and referenced to the standard path (figure 3). For measurements of R_E , substituting limbs and trunk paths does not significantly alter the overall path R_E , for any of the whole body paths except the ankle-to-ankle path which is noticeably lower, consistent with results from the regression model. For the wrist-to-wrist path, the higher resistance of the arms seems to be compensated by a lower measured resistance for a current crossing the trunk from wrist-to-wrist than from wrist-to-ankle.

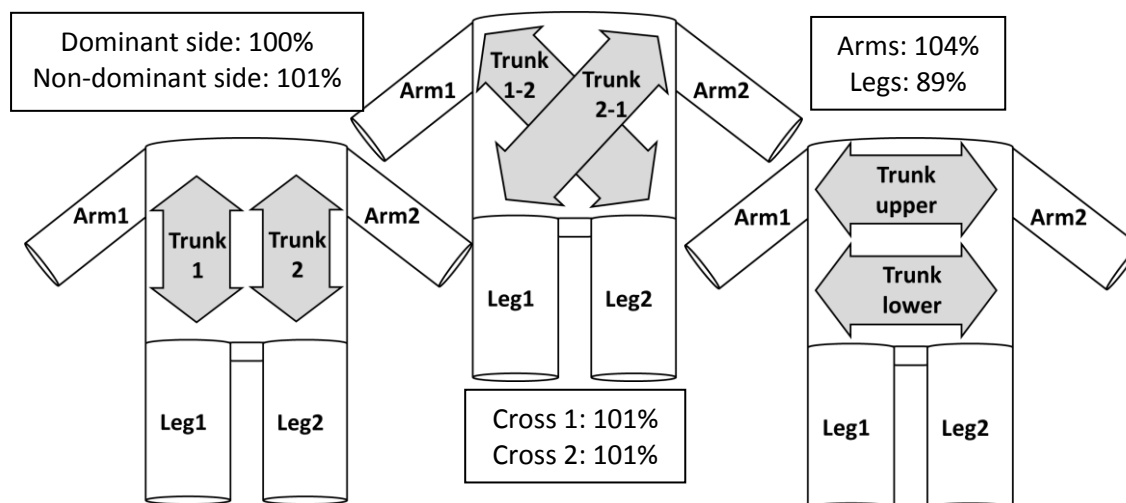


Figure 3: Re-calculating whole-body assessments of R_E expressed as a % of the standard measurement path (wrist-to-ankle on the dominant side) in healthy controls based on the data in table 5

For haemodialysis patients, it has been suggested that the presence of vascular access in a patients' arm can bias measurements of OH and so guidance suggests avoiding these paths. The evidence supporting this recommendation comes from studies using different bioimpedance with different analysis techniques to the BIS used in the BCM. Woodrow et al. used whole-body, single frequency BIA measurements to show decreased resistance in the fistula arm that was accompanied by increased arm circumference, suggesting increased excess fluid (Woodrow et al., 1997), although this was not replicated in paediatrics (Avila et al., 2015). More recently, two studies from a single centre using segmental BIA (SBIA) have reported that water and lean tissue content is different in the fistula and non-fistula arms (Panorchan et al., 2015, Booth et al., 2011). However, neither BIA or SBIA can adequately distinguish excess fluid from lean and adipose tissue, which left the possibility that the differences observed relate to differences in lean tissue alone rather than excess fluid, particularly given that fistulae tend to be placed in the non-dominant arm of patients. The results here confirm that the presence of a vascular access does tend to increase OH. However, the effect (mean: 0.4; 95% CI: 0.1 to 0.8 litres) is arguably negligible from a clinical perspective, when considering the overall uncertainty in target weight prescription.

Considering the model results for LTM and ATM in controls, it is important to note that the equivalence of OH across different paths does not translate to these compartments. Where accurate monitoring of body composition is important, the standard pathway is preferred and consistency is important. The dominant side has significantly increased LTM and reduced ATM as compared to the non-dominant side and the legs have increased LTM and reduced ATM compared to the arms (see Appendix 3). This is consistent with previous work using BIA on controls that demonstrated decreased resistance in the dominant arm compared to the non-dominant arm (Bedogni et al., 2002) and a decreased resistance of the

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3 legs compared to the arms (Lorenzo and Andreoli, 2003) as decreased resistance is linked
4 with greater muscle mass through the higher proportion of water in muscle than fat.
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7 *Use of post-dialysis measurements*

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9 Considering the use of post-dialysis BCM measurements, change in body weight was
10 compared to change in BCM-measured OH as there is no accepted gold standard measure of
11 OH to validate post-dialysis measurements. In theory, the change in OH over dialysis should
12 equal the change in body weight, while there should be no change in LTM or ATM. However,
13 dialysis has been shown to perturb fluid distributions (Shulman et al., 2001) which can
14 influence whole-body bioimpedance measurements (Zhu et al., 1999). Fluid shifts from the
15 limbs into the trunk manifest as an apparent decrease in ECF when measured by whole-
16 body techniques and shifts from the trunk to the limbs as an increase in ECF (Lundvall et al.,
17 1996).
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23 The results here suggest that post-dialysis BCM-measured OH has a small bias of around 0.3
24 litres, with limits of agreement of -1.9 to 1.3 litres. This supports the validation literature of
25 the BCM which has shown that the change in BCM-measured OH over dialysis is comparable
26 to the ultrafiltration volume (Wabel et al., 2007). There are reasonably large limits of
27 agreement which should be taken into account when making post-dialysis measurements,
28 but these measurements were taken immediately after dialysis and it is reasonable to
29 assume that they would be reduced if there was a time delay introduced between dialysis
30 end and BCM measurement, as recommended by the manufacturer. El-Kateb et al. reported
31 a similar dataset to that presented here (El-Kateb and Davenport, 2015) with contrasting
32 results, including a significant bias and limits of agreement three times larger than those
33 observed in this study. This discrepancy seems likely to be due to artefactual BCM
34 measurements and highlights the need for some expertise when making measurements
35 (Lindley et al., 2015). The BCM validation literature also suggests that a bias is introduced
36 into measurements of LTM and ATM when measurements are made immediately after
37 dialysis but within 30 minutes this becomes non-significant. Considering this, and the
38 findings here, users should have a degree of caution using BCM-measured LTM and ATM
39 from post-dialysis measurements.
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48 Despite the good agreement between change in BCM-measured OH and change in weight,
49 the model for OH did suggest there was a degree of ultrafiltration induced changes in fluid
50 distribution, with a larger change in the lower limbs than the upper. This would suggest that
51 relatively more fluid is recruited from the legs than the upper body which is largely in
52 agreement with previous work. Measurements over the first 75 minutes of dialysis using BIS
53 (Shulman et al., 2001) and over the whole haemodialysis session using SBIA (Zhu et al.,
54 2008) and segmental BIS (Chanchairujira and Mehta, 2001) have demonstrated a greater
55 fractional change in fluid in the legs as compared to arms and trunk. Abbas et al (Abbas et
56 al., 2014) showed that there is a greater percentage removal of ECF from the legs than other
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3 compartments but that as ultrafiltration rate is increased, there is a preferential recruitment
4 of fluid from the trunk.
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7 *Study limitations*

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9 The study was not powered to address the multiple comparisons made by the models - the
10 sample size was based on comparisons between the two primary whole-body paths only. A
11 larger sample would allow better estimates of these different estimates. It would also have
12 been interesting to extend the analysis to a group of haemodialysis patients who are
13 defined as being prone to intradialytic hypotension (IDH), to investigate the relationship
14 between fluid distributions, fluid dynamics and IDH.
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18 **Conclusions**

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21 In summary, these data helps BCM users make measurements and interpret results with
22 greater confidence. Measurement protocols can be more flexible and individualised than
23 the manufacturer's guidance suggests, which will help as many patients as possible benefit
24 from the technology. This is based on a number of key observations:
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- 27 • Any of the whole body paths other than ankle-to-ankle can be used as an alternative
28 to the standard path for measurement of OH by BCM, with an acknowledgement of
29 the additional uncertainty when interpreting the results.
- 30 • BCM-measured OH is greater when measuring across a site of vascular access, but
31 the increase arguably is not clinically significant when the uncertainty in other
32 methods of target weight assessment is considered.
- 33 • Making BCM measurements post-dialysis introduces a negligible bias to OH
34 measurements but does increase measurement uncertainty, which should be
35 accounted for when interpreting such data. This uncertainty will be reduced with
36 time after dialysis, such as asking patients to move off the dialysis station to be
37 weighed, before a measurement is made.
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52 Appendix 1

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54 The bespoke analysis programme for the 8-electrode BCM data was validated by re-
55 analysing data that had been used in standard BCM measurements. The raw data from
56 twenty measurements on subjects with a wide variety of body composition and fluid status
57 (mean (range) of BMI: 29 (16 to 50) kg/m²; and of OH 0.5 (-3.8 to 5.9) litres) were analysed
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3 with the programme and the agreement between the body composition parameters can be
4 seen in figure A1. For OH, the bias was 0.1 litres with 95% limits of agreement of around -0.1
5 to 0.3, showing very good agreement and verifying that the programmes are working
6 similarly to commercial device analysis. For LTM and ATM, biases of -0.4 and 0.3 litres were
7 observed with slightly larger confidence intervals. This is likely to be related to known issues
8 in modelling R_i which has a larger influence on LTM and ATM than OH. However, for the
9 purposes of the study LTM and ATM are secondary outcome interests and the agreement
10 was deemed sufficient.
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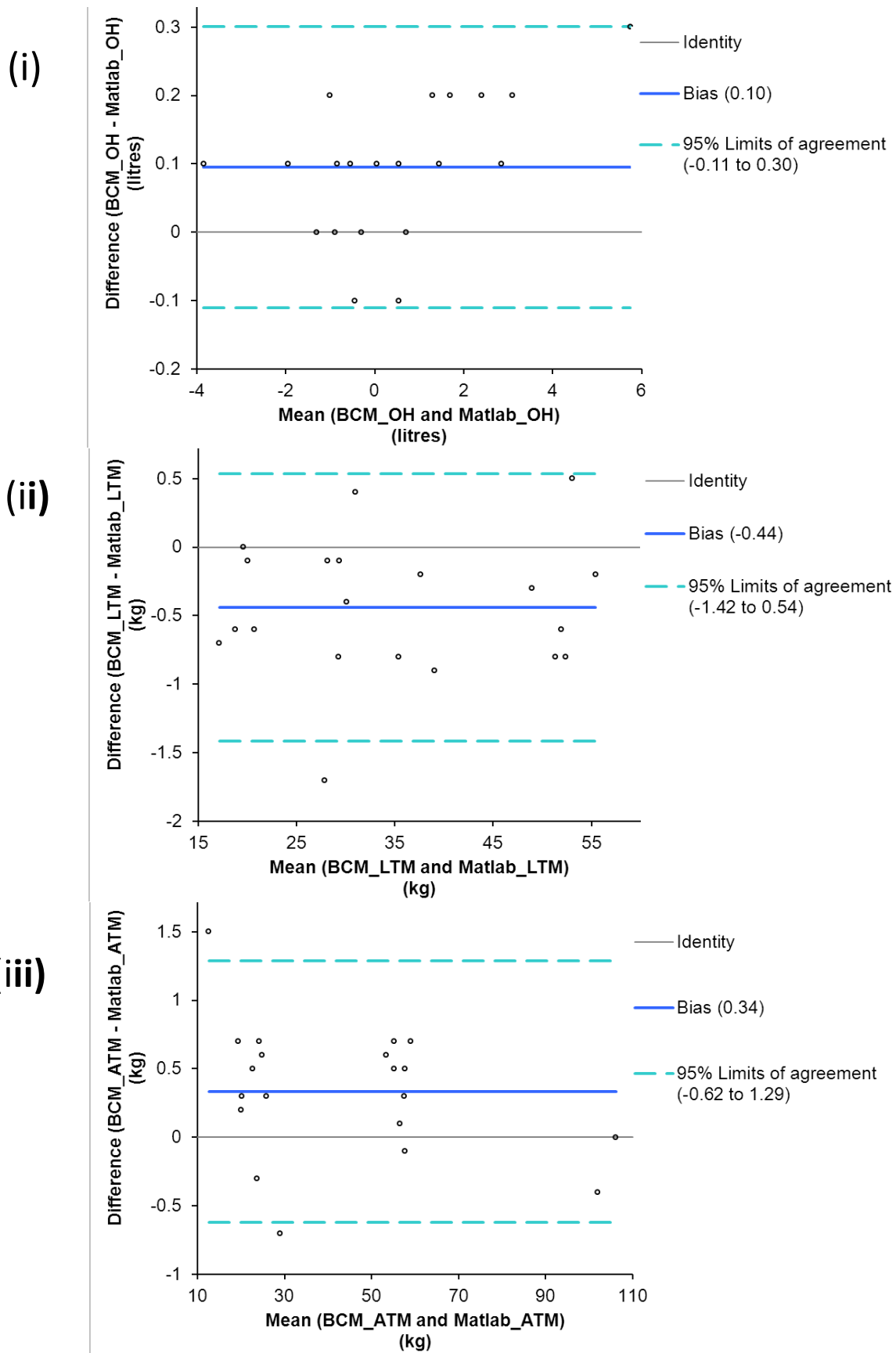


Figure A1: Validating the data analysis programme against commercial analysis for OH (i), LTM (ii), ATM (iii) using Bland-Altman analysis

Appendix 2

The results from checks of each of the models can be seen in figures A2 - A4. Visual inspection of the residual plots suggested random scatter. Although Q-Q plots showed some dispersion from normality; sensitivity analyses were done by checking the outliers for errors, but no clear problems with the data were found.

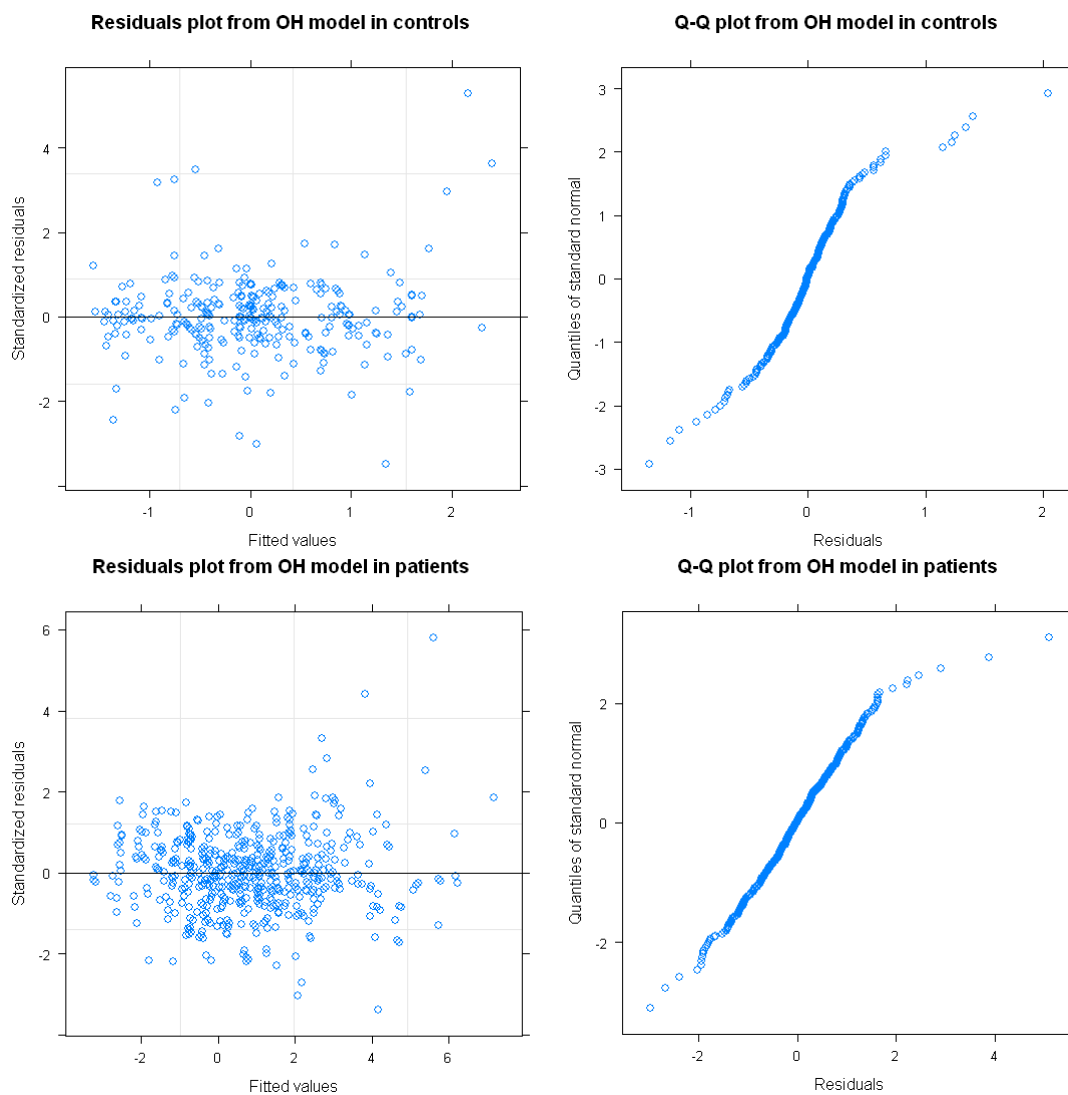


Figure A2: Plot of residuals (left) and a 'Q-Q' plot of the residuals (right) for mixed-effects model of OH in healthy controls (above) and haemodialysis patients (below). See appendix 2 for similar plots of the models for LTM and ATM

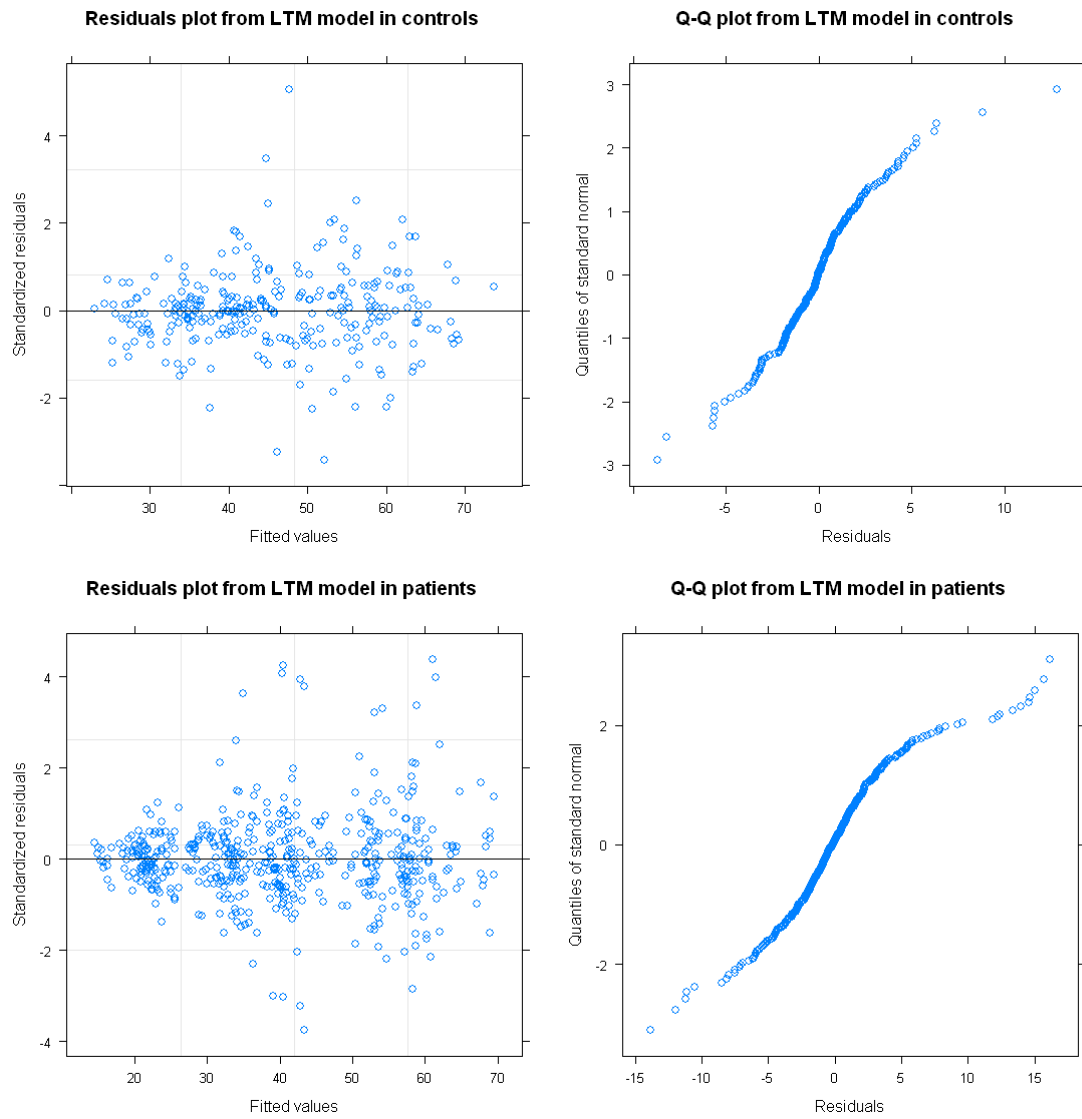


Figure A3: Plot of residuals (left) and a 'Q-Q' plot of the residuals (right) for mixed-effects model of LTM in healthy controls (above) and haemodialysis patients (below)

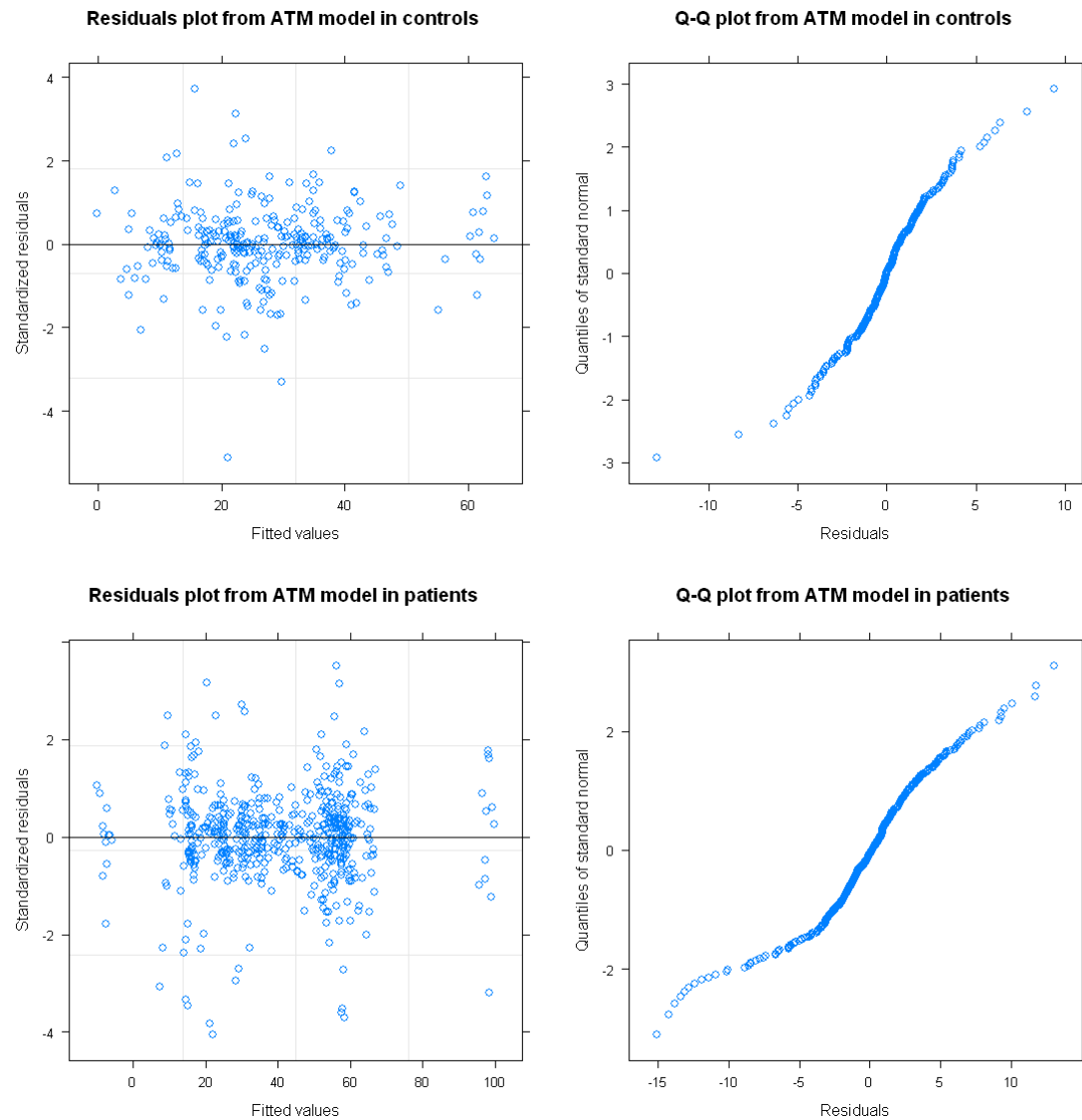


Figure A4: Plot of residuals (left) and a 'Q-Q' plot of the residuals (right) for mixed-effects model of ATM in healthy controls (above) and haemodialysis patients (below) Results of the mixed models for LTM and ATM for both healthy controls and dialysis patients.

Appendix 3

Results of the regression models for LTM and ATM for healthy controls (Tables A1 and A2) and dialysis patients (Tables A3 and A4).

	Measurement Path	LTM (kg)	Difference (kg)	p-value	Approx. 95% CI
Healthy controls	Dominant	45	-	<0.01	39 to 50
	Non-dominant	-	-1.5	<0.01	-2.5 to -0.4
	Cross1	-	-0.43	0.41	-1.4 to 0.59
	Cross2	-	-1.1	0.05	-2.1 to -0.03
	Arms	-	-2.7	<0.01	-3.7 to -1.7
	Legs	-	4.4	<0.01	3.4 to 5.4

Table A1: Model for LTM in healthy controls. Data are presented for a 60 year old female, where the adjustment for LTM with age was -0.17 per year (p<0.01; 95% CI: -0.28 to -0.07) and with sex was 19 for male (p<0.01; 95% CI: 15 to 22)

	Measurement Path	ATM (kg)	Difference (kg)	p-value	Approx. 95% CI
Healthy controls	Dominant	23	-	<0.01	12 to 35
	Non-dominant	-	1.4	<0.01	0.36 to 2.4
	Cross1	-	0.44	0.40	-0.57 to 1.5
	Cross2	-	0.95	0.07	-0.06 to 2.0
	Arms	-	2.7	<0.01	1.7 to 3.7
	Legs	-	-5.2	<0.01	-6.3 to -4.2

Table A2: Model for ATM in healthy controls. Data are presented for a 60 year old female, where the adjustment for ATM with age was 0.11 per year (p=0.33; 95% CI: -0.11 to -0.32) and with sex was -2.7 for male (p=0.44; 95% CI: -9.7 to 4.2)

	Measurement Path	LTM (kg)	Difference (kg)	p-value	Approx. 95% CI
Pre-dialysis	Non-VA side	29	-	<0.01	25 to 33
	VA-side	-	0.36	0.50	-0.68 to 1.4
	Cross1	-	-0.31	0.55	-1.4 to 0.73
	Cross2	-	0.74	0.17	-0.31 to 1.8
	Arms	-	1.2	0.03	0.16 to 2.3
	Legs	-	1.6	<0.01	0.57 to 2.6

Table A3: Model for LTM with dialysis patients. Data are presented for a 60 year old female, where the adjustment for LTM with age was -0.40 per year (p<0.01; 95% CI: -0.56 to -0.25), with sex was 17 for male (p<0.01; 95% CI: 12 to 22) and with post-dialysis measurements was -0.40 kg; p=0.1; 95% CI:-1.1 to 0.1 as compared to pre-dialysis

	Measurement Path	ATM (kg)	Difference (kg)	p-value	Approx. 95% CI
Pre-dialysis	Non-VA side	39	-	<0.01	30 to 47
	VA-side	-	-0.86	0.11	-1.9 to 0.19
	Cross1	-	0.27	0.61	-0.78 to 0.33
	Cross2	-	-1.2	0.02	-2.3 to -0.17
	Arms	-	-1.2	0.03	-2.2 to -0.11
	Legs	-	-3.1	<0.01	-4.2 to -2.1

Table A4: Model for ATM in dialysis patients. Data are presented for a 60 year old female, where the adjustment for ATM with age was 0.15 per year (p=0.40; 95% CI: -0.20 to 0.50), with sex was 3.9 for male (p=0.50; 95% CI: -7.5 to 15) and with post-dialysis measurements was 0.77 kg; p=0.01; 95% CI: 0.16 to 1.4 as compared to pre-dialysis

Appendix 4

Abbreviation	Description
ATM	Adipose tissue mass
BCM	Body Composition Monitor
BIA	Bioimpedance analysis
BIS	Bioimpedance spectroscopy
BMI	Body mass index
ECF	Extracellular fluid
ICF	Intracellular fluid
IDH	Intradialytic hypotension
LTM	Lean tissue mass
OH	Overhydration
R _E	Extracellular resistance
R _I	Intracellular resistance
SBIA	Segmental bioimpedance analysis
VA	Vascular access

Table A5: Abbreviations