Bioimpedance index for measurement of total body water in severely malnourished children: assessing the effect of nutritional oedema

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Introduction

Restoration of body composition indicates successful management of severe acute malnutrition (SAM), but no easy and accurate method is available (1–3). Bioimpedance method (BIM), whole-body (4) or segmental (5), is a safe, rapid and easy technique often used to predict total body water (TBW) and lean mass can in healthy individuals. However, its conventional application, commonly referred to as bioimpedance analysis (BIA), requires population-specific equations (6,7), and its accuracy is limited in general (8). This is due in part to inter-individual variability in body proportions (e.g. limb lengths), as narrow cylinders such as limbs contribute disproportionately to total body impedance (9). In healthy children, age or body size-to-age variation in impedance (Z in Ohm) could affect accuracy of TBW prediction (10). Stunted children with some degree of wasting produce higher R compared with anthropometrically normal children (11) and thus reflects the influence of abnormal body composition and/or body proportion. The poorer the ability of BIA to predict TBW, the less suitable it will be for clinical monitoring of body composition.

In most four-electrode (tetrapolar) measurements, Z is measured with 800µA alternating current at 50 kHz passing through the body, between the wrist and ankle (12). Two relationships between the Z of the body and its volume (V) are central to this method (4). First, derived from Ohm's Law, V is inversely related to Z and directly to conductive distance, approximated by height or length (H): $V = \rho H^2/Z$. Tissue specific resistivity, ρ, is a frequency-dependent constant inversely related to the number of free ions per V (13). Theoretically it is independent of body size, shape and age but could be affected by abnormal tissue hydration and/or osmolality (10–12). Second, at low frequencies electric current flows around the cell without penetrating into the cell, whereas at high frequencies the membrane capacitance is no impediment to the current and it flows indiscriminately through both intracellular and extracellular space, and thus assumed to reflect TBW better (4).

Decreased total body potassium, increased total body sodium and increased TBW are well recognized and common features of SAM, and often indicate diminished body cell mass and expanded extracellular fluid (1,2,16). Yet, how these abnormalities, particularly oedema, affect the performance of BIA is little studied. This study explores the performance of BIA in estimating TBW in children with SAM and the influence of oedema, using deuterium dilution method as a reference.

Subjects and Methods

Study setting and subjects

Children 0.5-14 years of age with SAM (MUAC <11.0 cm or weight-for-height <70 % of the median of the NCHS growth reference and/or nutritional oedema) admitted to Jimma University Hospital were included after informed consent. Children with life threatening conditions such as shock were excluded.

Data collection

Weight was measured to the nearest 10 g using a digital scale (Tanita BD 815 MA, Tokyo, Japan) and length to nearest 0.1 cm using a length board (SECA 416, Hamburg, Germany) for children less than 2 years of age. For older children, height was measured using stadiometer (SECA 214, Hamburg, Germany) to nearest 0.1 cm. Pitting oedema was checked by gentle pressure with the thumb on the feet for 3-5 seconds.

TBW was determined by deuterium dilution at a dose of 0·5g of $^{2}H_{2}O$ (Sercon, Crewe, UK) per kg body weight diluted in 5 ml of sterile water. Older children drank the deuterium whereas for younger children it was dripped into the mouth using a plastic tube attached to a syringe. Any spillage was collected in a tissue, weighed and subtracted from the dose. Pre-dose, and 3-hour post-dose samples of saliva were collected in all children. An additional 4-hour post-dose sample was collected in 15 children. In two children (1 with oedema), samples were collected hourly till 8-hour post-dose. Children were not given feeds 30 minutes before and 15 minutes after deuterium dosing. Saliva samples were kept at -20^{o}C before shipment to the UK for analysis. Though the dose used was based on Fourier transform infrared (FTIR) protocol, it was difficult to get the minimum (2 ml) saliva volume required for this method(17) and analysis was therefore undertaken at Institute of Child Health, UK using isotope-ratio mass spectrometry (Delta Plus XP; Thermofisher Scientific, Bremen, Germany). Samples were analysed in duplicate, with all enrichments normalized to values for international standard water samples, and the average value used in subsequent calculations. The mean precision of ^{2}H analyses was, 9.4 deltas, inducing imprecision on TBW of 0·8%. For calculating TBW, it was assumed that ^{2}H dilution space overestimated TBW by a factor of 1·044(ref. 16).

A tetrapolar portable bioimpedance (BI) analyser (BODYSTAT QuadScan 4000, British Isles, England), emitting 200 µA root mean square alternating current at 5, 50, 100 and 200 kHzs, was used to measure resistance (R), reactance (Xc) and Z. Self-adhesive disposable electrodes were attached at the right hand and foot, injecting leads were connected to the electrodes just behind the finger and toe and the measuring leads were then connected to the electrodes on the right

wrist and right ankle. Measurement was done after deuterium dosing and in triplicate, 5 minutes apart, while children were calm and supine on stretcher with limbs abducted from the body. Triplicate values were averaged for each subject.

Among 7 oedematous children with TBW data at 3 and 4 hours, there was an average increase in isotopic enrichment, which indicated a delayed deuterium equilibration time. The calculated TBW values therefore decreased during this period by 3.5% (95% CI: -10.6, 3.4). Among 7 non-oedematous children, there was no average change in TBW calculated from 3- and 4-hour post dose samples (average difference -0.2%, 95%CI -5.4, 5.0). Data on deuterium enrichment up to 8 hours in two children are shown in **Figure 1**. In the non-oedematous child, enrichment declined from 3 hours, indicating equilibration by 3 hours and subsequent dilution of body water by fluid intakes. In the oedematous child, enrichment increased between 3 and 4 hours, and then declined. This suggests that equilibration was complete by 4 hours in this child. On this basis, we assumed that all oedematous children were equilibrated by 4 hours. Therefore, 3-hour TBW values were reduced by 3.5% in all children with oedema, but no adjustment was made to the 3-hour TBW values in the non-oedematous children.

The study was approved by the Research Ethical Review Committee, College of Public Health and Medical Sciences, Jimma University. Before giving consent, caretakers were given verbal and written information. All the data were collected by two research nurses. The study was conducted from December 2009 to October 2011.

Statistics and data handling

Data were double entered into EpiData version 3.1 (EpiData Association, Odense, Denmark) and analysed with Stata/IC 12.1 (StataCorp, Texas, USA). Anthropometric z-scores, based on WHO child growth standard, were calculated in Stata and WHO Anthro Plus v 1.0.3 (WHO, Geneva, Switzerland)(19). BI index H^2/Z (cm^2/ohm) was calculated, where H is height or length. TBW from deuterium was regressed on BI index for SAM children as a single group, and separately for oedematous and non-oedematous. Then their regression coefficients and slopes were compared. Data were also expressed graphically, using the bioimpedance vector analysis (BIVA) approach of Piccoli (20). This approach, through RXc plot, allows axes of variability in the magnitude and hydration of lean tissue to be visualized. Xc and R were height-indexed (Xc/H, ohm/m and R/H, ohm/m), and Xc/H plotted against R/H.

Results

The study comprised 16 non-oedematous and 19 oedematous children with SAM and having median (interquartile range) age of 42 (26-54) months 48 (26-60) and 36 (30-48) months, respectively (**Table 1**). The minimum and maximum ages of the children were 10 month and 144 months, respectively. Both non-oedematous and oedematous children were severely stunted (p=

0.70), but the latter had higher BMI-for-age ($p<0.001$). As shown in **table 2,** the primary BI parameters (Z, R and Xc) were lower among oedematous children compared with non-oedematous, even when adjusted for height ($p<0.001$) whereas the BI indices at the two frequencies were not different between the two groups ($p>0.086$).

Results of the regression of TBW on BI indices for SAM children as a single group and separately for oedematous and non-oedematous are shown in **Table 3**. In the single group, there were marginal differences in the estimates between the two frequencies. In each separate group, all the regression estimates were similar for the two frequencies, and the intercepts were also comparable. This indicates that little is gained by using 200 kHz, and further analyses described below were therefore undertaken using Z50 only. The non-oedematous children had about 60% higher coefficient of determination (R^2) and 20% lower standard error of estimate (SEE) than oedematous children, indicating a much tighter association between BI indices and TBW than in oedematous children.

Although the difference in slopes between oedematous and non-oedematous group was not significant (**table 3**), for a given amount of TBW, oedematous children had a lower Z value and hence higher index (**Figure 2**). Additionally, in Figure 3 it is evident that the contrast in the slopes between oedema and non-oedema declines slightly at Z200 compared to Z50. So, there is a weak indication that at higher frequencies, where the current passes through both extracellular and intracellular space, the impedance-TBW association is not quite so different as when the current mainly passes through ECW. Using BIVA approach, the oedematous and non-oedematous children showed contrasting association between height-adjusted Xc and R (**Figure 3**).

Discussion

In this study the poor agreement between TBW and the BI index showed the complexity of assessing TBW in SAM patients, particularly among oedematous children. Fluid and electrolyte abnormalities in SAM might alter tissue electrical properties and thus make prediction of TBW using the BI index invalid.

Deuterium equilibration was delayed in oedematous (4hr) but not in non-oedematous children (3hr). This reflects and confirms the hemodynamic abnormality in children with SAM; analogous to hypothyroidism, they are characterized by significant prolongation of circulation time and expanded extracellular water(21). The longer equilibration duration among oedematous children could be explained by their excess ECW, which is clinically evident as oedema. This is a methodological issue which can thus be resolved by adapting the protocol; a separate issue is whether the association between the BI index and TBW is also affected by oedema.

In this study, oedematous children were found to produce lower impedance per unit of height, although they were as severely stunted as the non-oedematous children. Walker el al (11) showed that stunted Jamaican children have higher R than the non-stunted despite having the same TBW%. However, in the current study stunted children with oedema had lower BI parameters. The lower ρ, as estimated from the regression coefficients, may explain this difference. Theoretically ρ varies with frequency but not the size and shape of individuals (13). Alterations in the amount and composition of extracellular fluids, expected to be extreme in oedematous children, influence tissue-specific resistivity (22). The variations in the RXc plot between oedematous and non-oedematous may further support difference in their lean tissue hydration.

Regressing of TBW on H^2/Z appears to give weak predictive power generally for SAM. However, when the oedematous and non-oedematous children are analysed separately, the poor overall accuracy can be attributed primarily to a much looser fit between TBW and H^2/Z in the oedematous group (lower R^2 and higher SEE). The predictive power was similar between 200 kHzs and 50kHzs. The criteria for deciding on equations however is somehow empiric and also relies on the assumption that impedance has been measured equally well at each frequency(23). Our study suggests that BIA might help monitor TBW of non-oedematous children through treatment, but would be of less use in oedematous children. However, the hydration of lean tissue in non-oedematous SAM children is unknown (24) hence at present there is insufficient information to convert TBW to lean mass.

In conclusion, this study demonstrated that BI parameters were lower in oedematous compared with non-oedematous. Prediction of TBW using the BI index was unsatisfactory mainly among

oedematous SAM, but performed better in non-oedematous patients. Predictions of TBW at 200 kHz and 50 kHz didn't differ. The study also showed that isotope equilibration in children with oedematous SAM is delayed. Larger sample size and narrower age range could have demonstrated the variation in BIA prediction better. The potential utility of the BI index for monitoring changes in body composition in SAM patients therefore varies substantially between oedematous and non-oedematous children. Further work is required to develop BIA technology for clinical monitoring of these patients; in the meantime our equation for non-oedematous children may be valuable for research studies, but should not be applied in clinical practice.

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TG and JW were involved in the conception and design of the study. TG, PK and NW contributed to acquisition of data. TG and JW contributed to analyses and interpretation of the data. SE was responsible for saliva sample analysis using mass spectrometer.TG was responsible for write up of the paper while all co-authors reviewed the draft manuscript and accepted the final version.

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274

275

Fig 1. Patterns of deuterium enrichment (A) and corresponding calculated total body water (B) in two children with severe acute malnutrition. In Fig 1A, declines in enrichment can be attributed to post-equilibration fluid intake, whereas increases in enrichment indicate continuing isotopic equilibration. The data therefore indicate that the non-oedematous child was equilibrated by 3 hours, and the oedematous child by 4 hours.

Fig 2. Linear regressions of total body water using deuterium dilution on BI index (H^2/Z, cm^2/Ohm) of children with severe acute malnutrition, where H is height or length and Z impedance. The contrast in the slopes between oedema and non-oedema declines slightly at Z200 compared to Z50. The solid (non-oedematous) and broken (oedematous) lines represent the fitted values.

Fig 3. RXc plot of reactance (Xc) on resistance (R) of children with severe acute malnutrition by oedema. Height or length (H).

Table 1. Selected characteristics of children with severe acute malnutrition admitted to Jimma University Hospital by nutritional oedema [a]

	Non-oedematous (n=16)	Oedematous (n=19)	p-value
Age, month	48 (26 - 60)	36 (30 - 48)	0.01[b]
Sex, female	10 (62.5)	8 (42.1)	0.23[c]
Z- score [d]			
Height-for-age	-3.9 ± 2.8	-3.6 ± 1.7	0.70
Body mass index-for age	-4.3 ± 1.4	-1.5 ± 1.4	<0.001
Weight-for-age	-5.3 ± 1.5	-3.3 ± 1.6	<0.001

[a] mean ± SD or median (interquartile range) or n(%), [b] Kruskal-Wallis rank, [c] Chi-square and independent *t-test*

Table 2. Bioimpedance parameters and total body water of children with severe acute malnutrition by nutritional oedema [a]

	Non-oedematous n = 16	Oedematous n = 19	P - value
Impedance at 50kHz, Z50 (Ohm)	1128.9 ± 222.8	792.9 ± 197.8	<0.001
Impedance at 200khz, Z200 (Ohm)	1040.4 ± 199.2	752.1± 185.1	<0.001
Resistance, R50 (Ohm)	1117.5 ± 218.4	738.5 ± 215.2	<0.001
Reactance, Xc50 (Ohm)	56.0 ± 17.4	33.6 ± 14.9	<0.001
R50/H (Ohm/m)	1354.6 ± 374.6	872.6 ± 233.9	<0.001
Xc50/H (Ohm/m)	66.6 ± 22.1	40.0 ± 18.1	<0.001
$H^2/Z50$ (cm^2/ Ohm)[b]	7.4 ± 4.5	9.6 ± 2.6	0.09
$H^2/Z200$ (cm^2/ Ohm)	7.9 ± 5.0	10.0 ± 2.6	0.11
Total body water (L)	7.9 ± 3.2	8.2 ± 1.5	0.75

[a] Mean ± SD, total body water (TBW) using deuterium dilution and [b] height or length (H)

Table 3. Regressions of total body water using deuterium dilution on bioimpedance index (H^2/Z) by nutritional oedema of children (n=35) with severe acute malnutrition [a]

	Intercept	β(95%CI)	SEE	R^2
$H^2/Z50$ (cm^2/ohm)				
Both groups	2.70	0.50 (0.35 - 0.64)	0.07	0.59
Oedematous	3.72	0.35 (0.11- 0.60)	0.12	0.37
Non-oedematous	2.33	0.60 (0.39 - 0.81)	0.10	0.73
$H^2/Z200$ (cm^2/ohm)				
Both groups	2.50	0.48 (0.35 - 0.61)	0.06	0.65
Oedematous	3.43	0.36 (0.14 - 0.60)	0.11	0.38
Non-oedematous	2.27	0.55 (0.37 - 0.74)	0.09	0.76

[a] Height or length (H) / impedance (Z at 50 or 200 kHz), standard error of estimate (SEE) and coefficient of estimate (R^2). Intercepts and β (slopes) for oedematous and non-oedematous are not different between 50 kHz and 200 kHz, $p > 0.05$.

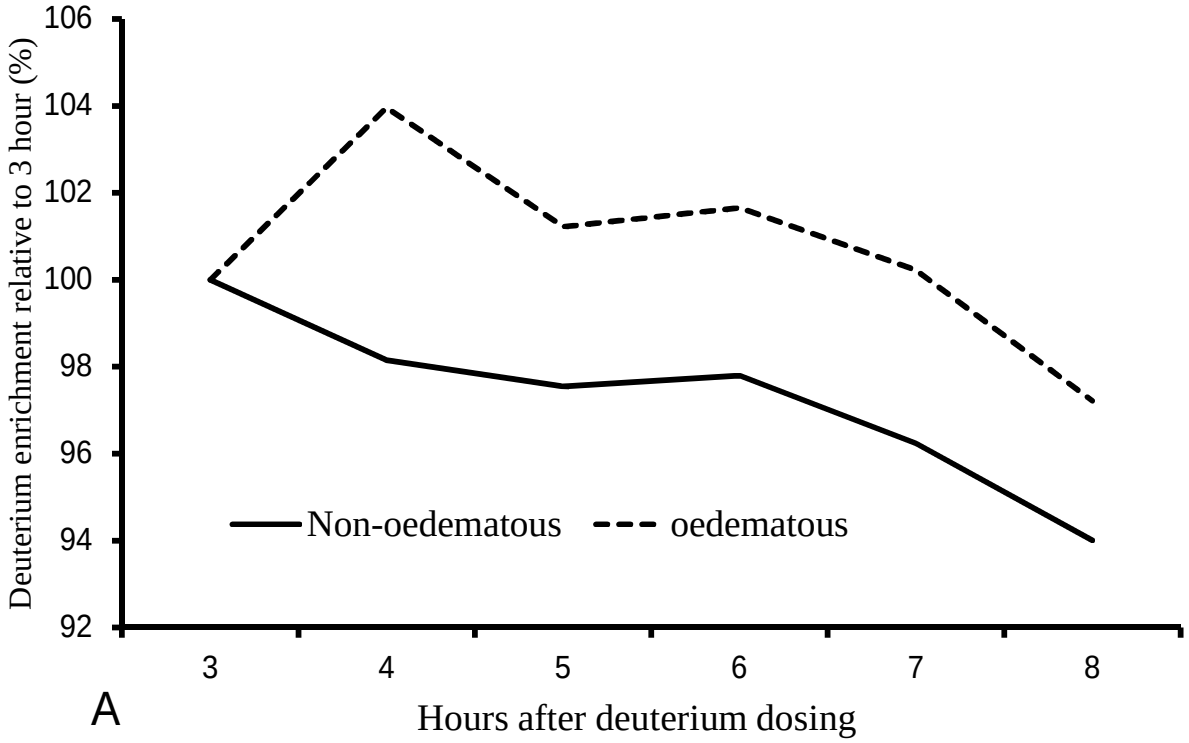
106
104
102
100
98
96
94
92
Deuterium enrichment relative to 3 hour (%)
Non-oedematous
oedematous
3
4
5
6
7
8
A
Hours after deuterium dosing

Fig 1A

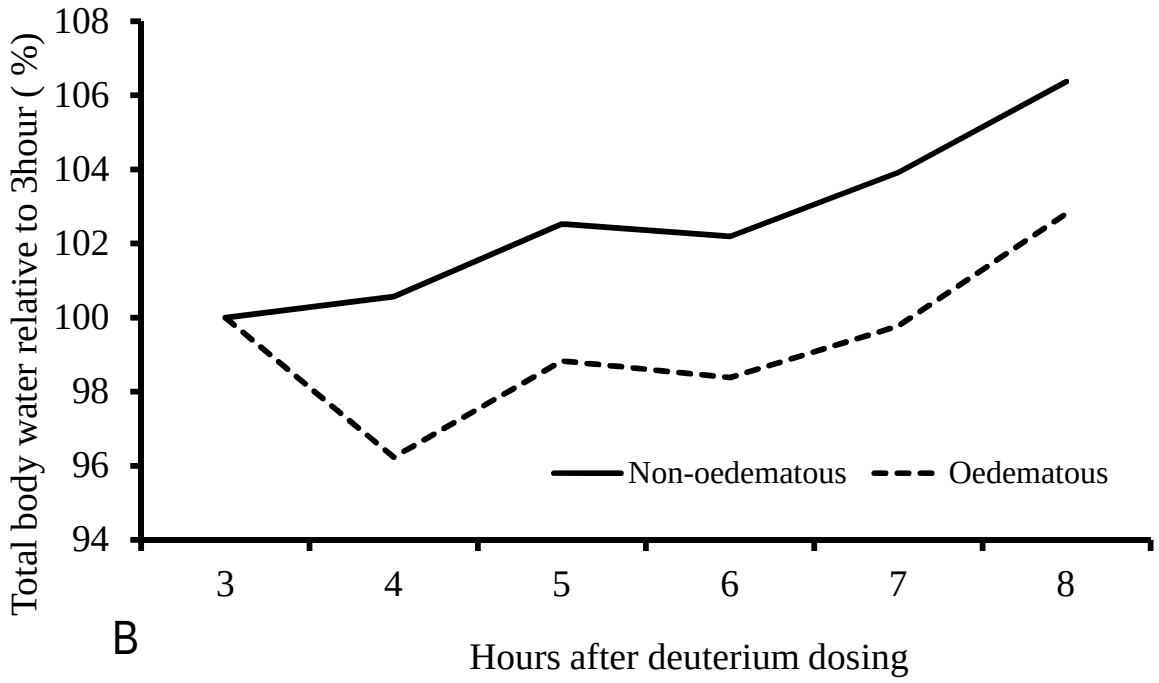
Total body water relative to 3hour (%)
108
106
104
102
100
98
96
94
3
4
5
6
7
8
Non-oedematous
Oedematous
B
Hours after deuterium dosing

Fig 1B

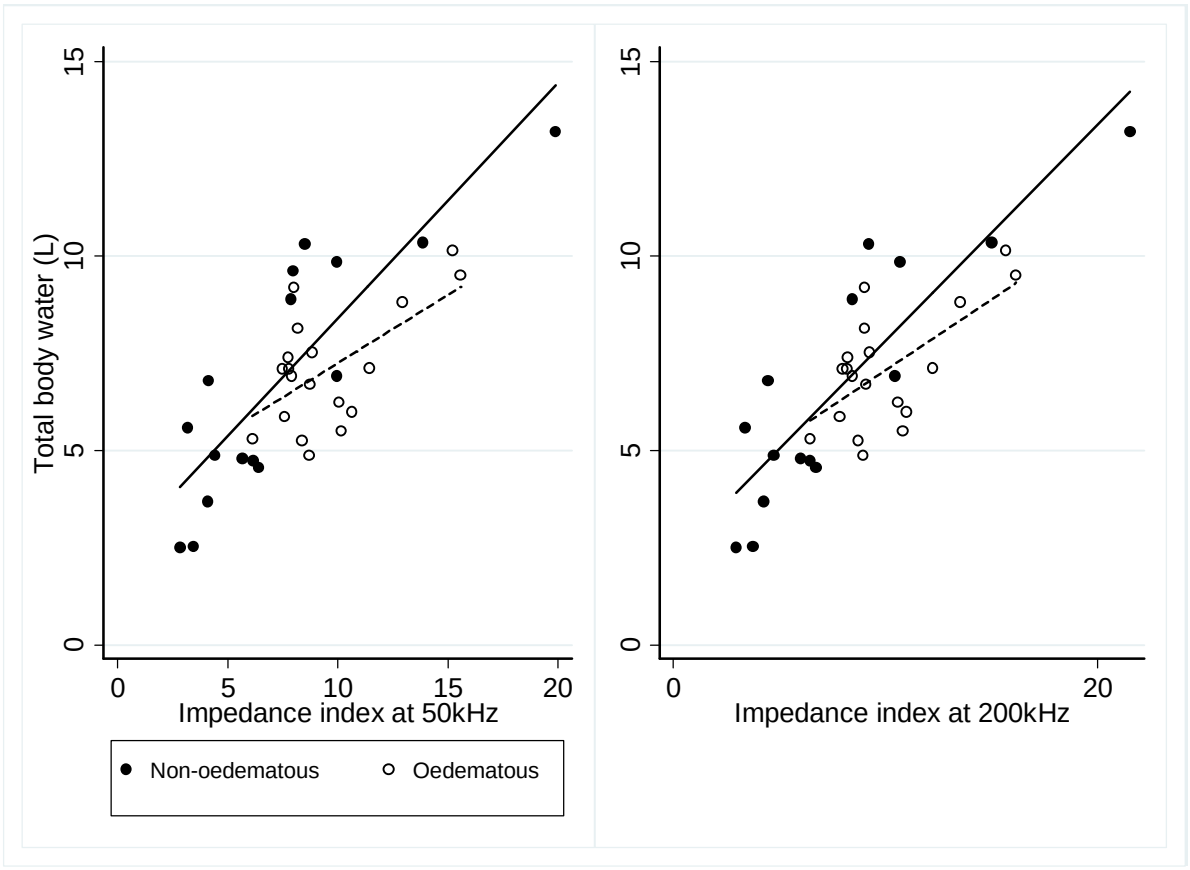
Total body water (L)
0
5
10
15
0
5
10
15
20
Impedance index at 50kHz
Non-oedematous
Oedematous
0
5
10
15
0
20
Impedance index at 200kHz

Fig 2

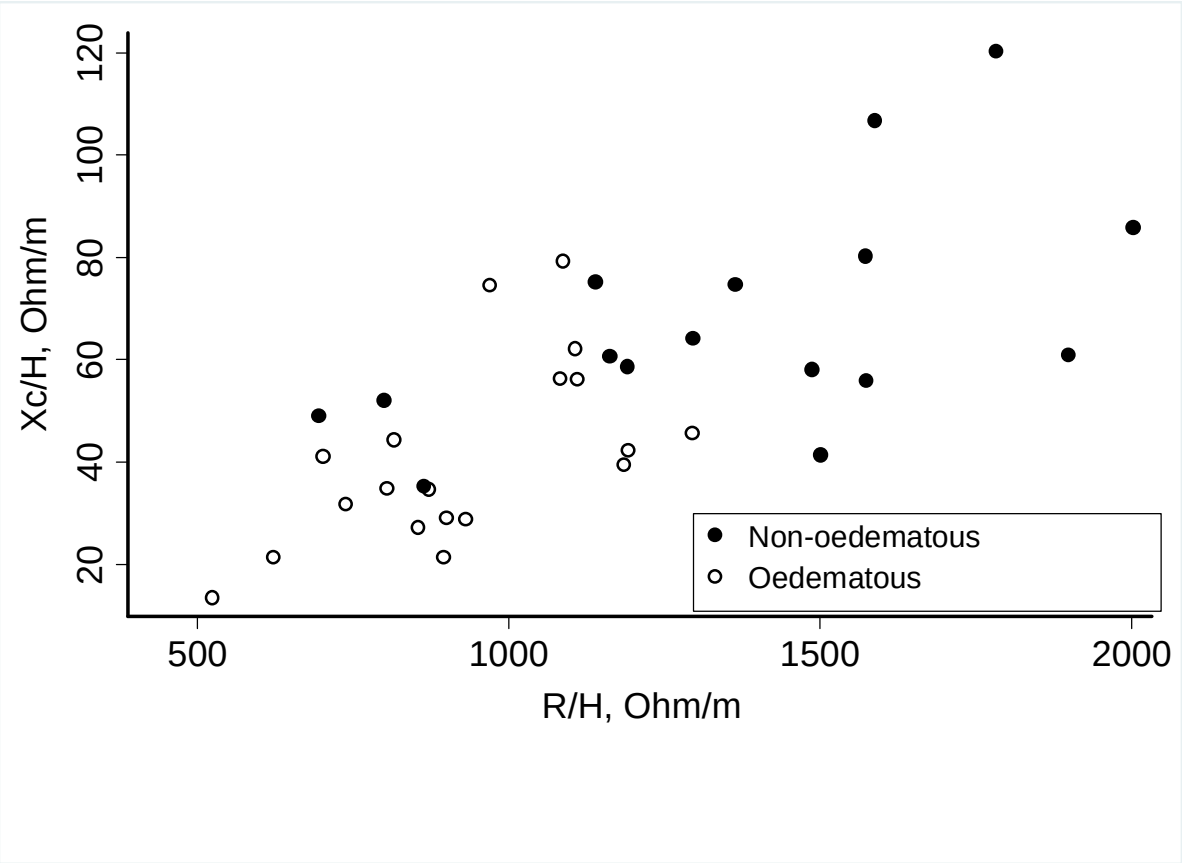
Xc/H, Ohm/m
20
40
60
80
100
120
500
1000
1500
2000
R/H, Ohm/m
Non-oedematous
Oedematous

Fig 3