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3 **Anthropometry-based equations to estimate body composition: a suitable**
4 **alternative in renal transplant recipients and patients with non-dialysis**
5 **dependent kidney disease?**
6

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17 **Abstract word count:** 288 **Manuscript word count:** 2666
18

19 **Short title / running head:** Body composition assessment in kidney disease
20

21 **Acknowledgements:** We gratefully acknowledge the Stoneygate Trust whom part-funded
22 this work. The research was supported by the National Institute for Health Research (NIHR)
23 Leicester Biomedical Research Centre (BRC). The views expressed in this publication are
24 those of the author(s) and not necessarily those of the NHS, the National Institute for Health
25 Research Leicester BRC or the Department of Health.

Support and Financial Disclosure: The authors declare no financial conflicts of interest.

Abstract

Objective: Chronic kidney disease (CKD) patients and renal transplant recipients (RTR) are characterized by aberrant body composition such as muscle wasting and obesity. It is still unknown which is the most accurate method to estimate body composition in CKD. We investigated the validity of the Hume equation and bioelectrical impedance analysis (BIA) as an estimate of body composition against dual-energy X-ray absorptiometry (DXA) in a cohort of non-dialysis dependent (NDD)-CKD and RTR.

Design: Cross-sectional study with agreement analysis of different assessments of body composition.

Setting: Secondary care hospital setting.

Subjects: 61 patients (35 RTR and 26 NDD-CKD).

Intervention: Body composition (lean mass (LM), fat mass (FM), and body fat % (BF %)) was assessed using multi-frequency BIA and DXA, and estimated using the Hume formula. Method agreement was assessed by intraclass correlation coefficient (ICC), regression, and plotted by Bland and Altman analysis.

Main outcome measure: Body composition.

Results: Both BIA and the Hume formula were able to accurately estimate body composition against DXA. In both groups, the BIA overestimated LM (1.7-2.1 kg, ICC .980-.984) and underestimated FM (1.3-2.1 kg, ICC .967-.972) and BF % (3.1-3.8 %, ICC .927-.954). The Hume formula also overestimated LM (3.5-3.6 kg, ICC .950-.960) and underestimated BF % (1.9-2.1 %, ICC .808-.859). Hume-derived FM was almost identical to DXA in both groups (-0.3-0.1 kg, ICC .947-.960).

Conclusion: Our results demonstrate, in RTR and NDD-CKD patients, that the Hume formula, whose estimation of body composition is based only upon height, body mass, age, and sex, may reliably predict the same parameters obtained by DXA. Additionally, BIA also provided similar estimates versus DXA. Thus, the Hume formula and BIA could provide simple and inexpensive means to estimate body composition in renal disease.

Keywords: chronic kidney disease; renal transplant; renal disease; body composition,

Introduction

Chronic kidney disease (CKD) is characterized by aberrant body composition, in particular, muscle and protein-energy wasting, and elevated levels of adiposity (1-3). Abnormal body composition is associated with malnutrition, reductions in physical function and quality of life (4), but are also independent risk factors for adverse clinical outcome and mortality (1, 2, 4-6). Depending on the criteria, ~9-30% of non-dialysis dependent (NDD)-CKD patients are ‘muscle wasted’ (2, 4, 5), with higher prevalence in more advanced stages (2, 4, 5).

Obesity is a major risk factor for cardiovascular disease (7-9), as well as higher CKD risk and quicker disease progression (9, 10). Whilst higher pre-transplant muscle mass is associated with greater post-transplant graft and patient survival (11), an increasing number of transplants are performed in obese recipients with more than 30% of renal transplant recipients (RTR) being obese (12, 13). Despite improved kidney function, obese RTR often have worse short-term outcomes including increased risk of delayed graft function and wound complications (7, 12, 14-16).

Due to the association with negative outcomes, assessing body composition is essential (2, 4, 17, 18). However, routine body composition measurement relies on the use of BMI. Although simple to calculate, requiring body mass (BM) and height, crude BMI phenotyping has inadequacies (19), especially in CKD (3, 12, 20-23). BMI is not able to distinguish low muscle mass from adiposity (20, 24), potentially masking ‘sarcopenic obesity’ (19).

The most appropriate method to estimate body composition in CKD is still unknown (18).

Two commonly cited methods are dual-energy X-ray absorptiometry (DXA) and bioelectrical

impedance analysis/spectroscopy (BIA/S) (2). Although DXA requires further investigation to be accepted as a 'gold standard' (25), the method is recognised to be precise (17, 19, 26-28) and recommended by clinical practice guidelines for nutrition in chronic renal failure (29). Whilst DXA and BIA/S have their relative strengths and inadequacies, their use is often limited by accessibility, cost, and requirement for trained personnel (2, 17-19, 26).

In clinical practice, measuring body composition should preferably be simple with a low risk of complications (2). Consequently, recent publications have recommended anthropometric estimates and algorithms as adequate alternatives. Whilst various such formulas exist, the Hume formula has been deemed superior when compared to DXA and CT imaging (26, 30). Utilising just BM and height (i.e. as BMI), along with sex and age, the Hume formula may provide an accurate classification of body composition. Unlike BMI, this may help differentiate CKD patients who are muscle wasted, potentially malnourished, and/or obese. This should help inform better clinical decisions in regard to treatment and prognosis.

Aim

The present study investigated the validity of the Hume equation as an estimate of body composition against a reference 'DXA' measurement in a cohort of NDD-CKD and RTR. We also explored the association between BIA and DXA in these groups. We hypothesized that both the Hume equation and BIA would be good estimates of body composition, and could offer simple, accessible, accurate, and important assessments of body composition in clinical practice.

Methods

Participants

Renal patients attending nephrology outpatient clinics, between September 2014 and October 2017, based at the Leicester General Hospital, Leicester, UK were approached to take part by their clinician. Exclusion criteria included: <18 years, pregnancy (contraindication to having a DXA scan), visual or hearing impairment, inability to give informed consent, and, if under the impression of clinician, unable to complete the trial protocol (e.g., completion of physical function tests pertinent to the main trial). RTR were required to be 6 months post-transplantation. This is an exploratory secondary-analysis of a recent trial conducted by our group looking at cardiovascular risk in patients with renal disease (ISRCTN 11615440). The study was approved by the East-Midlands Derby Research Ethics Committee (15/EM/1049) and conducted in accordance with the declaration of Helsinki.

Protocol and data collection

Clinical, anthropometric, and BIA measures were taken during a single visit to Leicester General Hospital or Glenfield Hospital, Leicester, with DXA performed separately ~1 week later. During this DXA visit, current body mass was re-assessed. Patients were advised to fast overnight prior to the assessment sessions and to wear light clothing. The anthropometric measurements and the BIA were performed by experienced researchers specializing in exercise physiology, whereas the DXA scan was performed by a trained technician. Patients were asked if they needed to void their bladder before each scan.

Outcome measures

Clinical and demographic parameters

Basic demographic information and clinical parameters were taken from medical records and routine blood tests.

Anthropometry

Height, BM, waist and hip circumference were measured in accordance with standard guidelines (31).

DXA

NDD-CKD patients were scanned on a GE Healthcare Lunar iDXA scanner (accommodated in the Leicester Diabetes Centre, Leicester General Hospital), and RTR were scanned on a GE Healthcare Lunar Prodigy (accommodated at Glenfield Hospital, Leicester). Excellent agreement and negligible differences between the two devices has been reported (32-34). DXA passes two X-ray beams of different energies through the body. The difference in attenuation of these two energies is related to the thickness, density, and chemical composition of the object traversed (35). This information is used to estimate the three body compartments of fat mass (FM) (including body fat % (BF %)), lean mass (LM), and bone content (19, 28).

BIA

Patients underwent multi-frequency BIA using an InBody 370 (CA, USA). Patients stood on the device barefoot and holding onto the handles. A small electrical current is passed through the body to estimate total tissue fluid content. Using this information, along with individual's general characteristics (e.g., sex, age, height, and BM), specific empirical equations are applied to provide estimates of body compartments (including FM, LM, BF %) (2, 19).

Hume formula

The Hume formula, developed in 1966 (36), was used to estimate LM. These sex-specific formulas require age, sex, height, and BM:

Male: $LM = (0.32810 * BM \text{ (kg)}) + (0.33929 * \text{height (cm)}) - 29.5336$

Female: $LM = (0.29569 * BM \text{ (kg)}) + (0.41813 * \text{height (cm)}) - 43.2933$

From this estimation of LM, FM (BM-LM) and BF % (FM/BM * 100) were calculated in accordance to Carnevale et al. (26).

Statistical analysis

Data for each method are reported as mean (\pm SD) and assessed using GraphPad Prism 7 and SPSS 24. Reliability of data was assessed using the intraclass correlation coefficient (ICC) (r) with 95% confidence intervals (95CI). An ICC between .600-.749 is considered 'fair', $\geq .750$ 'good', whilst a value $\geq .900$ is considered 'excellent' for clinical measures (37). Regression plots (r^2) were also used to estimate agreement between the methods, with a $P < .050$ indicating statistical significant correlation. Data is represented graphically as Bland-Altman plots with mean bias and limits of agreement (LoA) at 95CI (38). Here the difference between the two paired measurements is plotted against the mean of the two measurements. We determined that a minimum total sample size of 39 patients was needed to estimate an ICC r of .600 (the minimal acceptable ICC in clinical investigations (39) with a β of 0.80 at a significance level of $P < .050$ (40)).

Results

61 patients were recruited (35 RTR and 26 NDD-CKD). Full patient clinical and demographic characteristics are shown in **Table 1**. Cohorts were well matched for age, sex, and ethnicity. Patients represented a heterogeneous sample of CKD, and disease etiology represented an assortment of causes. The mean eGFR was 37.6 (± 24.1) mL/min/1.73m² in the NDD-CKD patients, and 53.6 (± 20.5) mL/min/1.73m² in RTR. RTR were an average 94.2 months (~8 years) post-transplantation.

DXA vs BIA

The means for LM, FM, and BF % for DXA and BIA can be found in **Table 2**. Mean bias and 95CI LoA taken from the Bland-Altman plots can be seen in **Figures 1** and **2**. All ICC values and r^2 values taken from regression modeling can be found in **Table 3**.

Overall, BIA was strongly comparable to DXA estimated body composition. In RTR, compared to DXA, BIA overestimated LM by 2.1 (-3.9 to 8.1) kg, although ICC ($r = .984$) showed ‘excellent’ agreement along with an r^2 value of 0.99. BIA underestimated FM (-2.1 (-8.6 to 4.3) kg) and BF % (-3.8 (-11.7 to 4.0 %)), although both showed ‘excellent’ (ICC $r = .972$ and $.954$) agreement, respectively. In the NDD-CKD patients, like the RTR, BIA tended to overestimate LM (1.7 (-3.9 to 7.2) kg) and underestimate both FM (-1.3 (-7.0 to 4.4) kg) and BF % (-3.1 (-9.0 to 2.9 %)). All showed ‘excellent’ (ICC $r = .980$, $.967$, and $.927$) agreement, respectively.

DXA vs Hume formula

204 The means for LM, FM, and BF % for DXA and the Hume formula can be found in **Table 2**.
 205 Mean bias and 95CI LoA taken from the Bland-Altman plots can be seen in **Figure 1** and **2**.
 206 All ICC values and r^2 values taken from regression modeling can be found in **Table 3**.
 207
 208 Like BIA, the Hume formula overestimated LM in both RTR (3.5 (-4.7 to 11.6) kg) and
 209 NDD-CKD (3.6 (-3.9 to 11.1) kg). However, both showed ‘excellent’ agreement (ICC $r =$
 210 .960 and .950). The Hume formula was able to estimate FM with remarkable accuracy
 211 compared with DXA. For RTR, Hume formula-derived FM was 0.3 (-8.0 to 7.3) kg
 212 difference (ICC $r =$.960 ‘excellent’), and in NDD-CKD only 0.1 (-7.7 to 7.9) kg difference
 213 (ICC $r =$.947 ‘excellent’). The Hume formula underestimated BF % for both the RTR (-2.1 (-
 214 13.2 to 8.9) %) and NDD-CKD (-1.9 (-10.3 to 6.6) %) groups. ICC r showed ‘good’
 215 correlation for both ($r =$.859 and .808).

216

Discussion

Our results demonstrate the Hume formula may reliably predict body composition as by DXA in RTR and NDD-CKD. Additionally, body composition estimated by BIA also provided similar estimates to DXA. Thus, the Hume formula and BIA could provide simple means to estimate body composition in renal disease. For the Hume formula, only height, BM, age, and sex are needed alongside to obtain such information. Using similar parameters, the Hume formula represents a superior source of body composition information than BMI.

Accurate body composition measurement is important in patients with renal disease. Patients not yet requiring dialysis and RTR are characterized by aberrant body composition changes, including muscle wasting (2, 4) and increased adiposity (10). These changes are associated with reductions in physical function, quality of life (4, 5), renal function (10), increased mortality and outcome (1, 2, 4-6), and for RTR, delayed graft function (7, 12, 14, 16).

In clinical practice, BMI remains the principal method to assess body composition, in particular categorizing obesity. However, BMI has several limitations, particularly in CKD (3, 7, 12, 19-23). Some research suggests an ‘obesity paradox’ exists in renal patients (i.e. obesity protects against mortality) (discussion of which is beyond the scope of this paper) (41, 42). However, inadequacies of BMI (specifically its inability to determine muscle mass) have been identified the source of this ‘paradox’ (3, 22, 41). This supports the need for better understanding of body composition measurement. Citing Prado and Heymsfield, “*if the medical fields have evolved to using sophisticated techniques, we can also advocate for the use of advanced body composition methodology for assessment of health status of patients beyond simple measurement of body weight*” (35).

242
243 DXA is considered a reference method for body composition assessment in clinical research
244 (26), and is recognised as accurate and reliable (17, 19, 26, 27). However, DXA use is limited
245 due to its accessibility, radiation, cost, time, and trained personnel requirement (2, 17, 18,
246 26). As such, there remains a need for simple and accessible tools for body composition
247 estimation in CKD. An alternative method may be BIA. BIA assesses FM and muscle mass
248 (2) by measuring the impedance of a small electric current to estimate fluid content. We
249 found in both RTR and NDD-CKD, BIA provided an accurate estimation of body
250 composition compared to DXA. BIA tended to overestimate LM (~2kg), and underestimate
251 both FM (~1-2kg) and BF % (3-4%). Underestimation of FM and BF % by BIA versus DXA
252 has been reported elsewhere (43). Our LM difference of ~2kg falls under the ± 5 kg deemed
253 'clinically acceptable' for such comparisons (30).

254
255 Our findings support previous research validating BIA against DXA in other clinical
256 populations (e.g., elderly (44) and obese patients (45)). However, some research evaluating
257 BIA has provided conflicting findings (46). Whilst data is limited in renal populations,
258 research in the late 1990's showed that multi-frequency BIA is not a valid tool to measure
259 body composition in RTR (15), and more recent research seems to confirm its lack of
260 agreement with DXA (18). These data seemingly oppose our and other findings (43, 46, 47).
261 BIA is still limited by fluid changes associated with renal disease (20, 28, 48), and its
262 accuracy can be altered via hydration status (19). In our study, patients were asked to attend
263 fasted to ensure hydration status effects were minimized. However, in NDD-CKD or RTR,
264 fluid disturbances may not represent such a problem compared to that experienced by dialysis
265 patients. In dialysis patients, studies have reported inaccuracy of BIA, particularly single
266 frequency BIA, on the assessment of body water (49, 50).

The Hume formula (developed in 1966) accurately estimated body composition against DXA. The Hume formula is only able to predict LM, but using BM, FM and BF % can be calculated. The Hume formula overestimated LM in our sample (~3.5kg); more than the overestimation by BIA (~2kg). Whilst LM estimation appears superior using BIA, Hume-derived measures of FM performed better. The Hume formula underestimated BF % by ~2% (compared to ~3-5% by BIA). Hume formula estimation of FM was almost identical to DXA; underestimating FM by 0.3kg in RTR and overestimating FM by just 0.1kg in NDD-CKD.

Whilst no previous research has attempted to validate the Hume formula against DXA in renal patients, research by Carvnevale et al. (26) showed the Hume formula is an accurate alternative to DXA in older adults with differences of ~1.5kg for LM and FM. In cancer patients, the Hume formula was the only acceptable height-and weight-based formula to adequately approximate LM against a CT; the James and Boer formulas were deemed inaccurate. The LM difference of 1.8kg was deemed clinically acceptable (defined as ± 5 kg) (30). Consequently, our difference of ~3.5kg can also be considered acceptable.

Importantly, the Hume formula uses the same parameters as BMI, with only age and sex needed additionally. All these variables are routinely collected. Our analysis found the LoA from Bland– Altman plots included zero; this excludes substantial biases for both the Hume formula and BIA, and both means appear to be valid alternative methods to estimate body composition in renal patients. For the Hume formula, no additional equipment is required.

Strengths and limitations

Our study is strengthened by the use of DXA as a reference of body composition, as well as investigating the comparison with BIA. Although two DXA scanners were used, excellent agreement between iDXA and Prodigy densitometers has been reported (32-34). Whilst this does not interfere with our intra-cohort analysis of the different methods, this should be taken into account when interpreting any differences in body composition between cohorts. We were able to recruit from two cohorts of renal disease – RTR and NDD-CKD, and across both cohorts we were able to recruit patients with a range of ages, renal function, and body composition. We are limited by our relatively small sample size, however, this exploratory analysis did reach the minimum total of 39 patients required to estimate an ICC r of .600 (the minimal acceptable ICC in clinical investigations (39)). Nonetheless, our sample gives a good indication of the accuracy of the Hume formula and BIA against DXA, but further research is needed to 1) clarify this finding, 2) determine the accuracy in detecting body composition changes following an intervention (e.g., exercise), and 3) determining whether these methods are viable in clinical practice.

Practical Application

The Hume formula may reliably predict the same parameters obtained by DXA in both RTR and NDD-CKD patients. Notably, the Hume formula does not require any additional equipment and utilizes routinely collected parameters including height and BM. With the addition of age and sex, this formula provides a superior wealth of body composition information over the routinely used, but largely inadequate, BMI. Additionally, body composition estimated by BIA also provided similar estimates versus DXA. Thus, both the Hume formula and BIA could provide simple and inexpensive means to estimate body composition in renal disease.

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- 448
- 449

450 **Table 1.** Patient characteristics

	RTR (n = 35)	NDD-CKD (n = 26)
Age (years)	51.6 (±12.0)	58.8 (±17.5)
Sex, n female (%)	12 (34%)	10 (38%)
BMI (kg/m ²)	26.3 (±4.3)	30.0 (±4.7)
Height (cm)	170.8 (±11.1)	171.1 (±8.1)
Body mass (kg)	77.3 (±17.8)	88.0 (±16.0)
Waist circumference (cm)	95 (±14)	103 (±13)
Hip circumference (cm)	101 (±10)	110 (±27)
Waist to hip ratio	0.95 (±0.10)	0.96 (±0.12)
Ethnicity		
White British, n (%)	25 (71%)	22 (85%)
White Other, n (%)	1 (3%)	0 (0%)
Asian, n (%)	9 (26%)	4 (15%)
Disease aetiology		
Diabetic nephropathy, n (%)	3 (9%)	4 (15%)
Interstitial nephritis, n (%)	2 (6%)	0 (0%)
IgA nephropathy, n (%)	4 (11%)	5 (19%)
Polycystic kidney disease, n (%)	9 (26%)	2 (8%)
Other, n (%)	11 (31%)	4 (15%)
Unknown / aetiology uncertain, n (%)	6 (17%)	11 (42%)
Months post-transplant	94.2 (±90.6)	-
Living donor	16 (46%)	-
Deceased donor	19 (54%)	-
Co-morbidities		
Diabetes mellitus type II, n (%)	9 (29%)	7 (27%)
Hypertension, n (%)	29 (50%)	18 (69%)
Heart disease, n (%)	4 (11%)	1 (4%)
Arrhythmia, n (%)	2 (6%)	3 (12%)
Liver disease, n (%)	0 (0%)	0 (0%)
Dyslipidaemia, n (%)	5 (14%)	2 (8%)
Clinical parameters		
eGFR (mL/min/1.73m ²)	53.6 (±20.5)	37.6 (±24.1)
Hb (mg/dL)	126.9 (±14.9)	130.8 (±14.9)
Albumin (g/L)	42.8 (±2.6)	42.4 (±3.6)
Urea (mmol/L)	10.2 (±4.9)	15.6 (±9.2)

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452 Unless stated, data presented as mean (±SD). RTR = Renal Transplant Recipients; NDD-CKD
453 = Non-Dialysis Dependent Chronic Kidney Disease; BMI = Body Mass Index; eGFR =
454 Estimated Glomerular Filtration Rate; Hb = Hemoglobin

455 **Table 2.** Means, and bias with limits of agreement between DXA, BIA, and the Hume formula

	DXA	BIA	Hume formula	DXA vs BIA	DXA vs Hume formula
	Mean (\pm SD)	Mean (\pm SD)	Mean (\pm SD)	Bias (LoA)	Bias (LoA)
RTR (n = 35)					
Lean mass (kg)	49.2 (\pm 11.4)	51.3 (\pm 13.1)	52.7 (\pm 9.7)	2.1 (-3.9 to 8.1)	3.5 (-4.7 to 11.6)
Fat mass (kg)	24.9 (\pm 9.9)	22.8 (\pm 9.9)	24.6 (\pm 9.9)	-2.1 (-8.6 to 4.3)	-0.3 (-8.0 to 7.3)
BF % (%)	33.1 (\pm 9.1)	29.3 (\pm 9.9)	30.9 (\pm 6.7)	-3.8 (-11.7 to 4.0)	-2.1 (-13.2 to 8.9)
NDD-CKD (n = 26)					
Lean mass (kg)	52.5 (\pm 9.3)	54.2 (\pm 10.5)	56.1 (\pm 7.8)	1.7 (-3.9 to 7.2)	3.6 (-3.9 to 11.1)
Fat mass (kg)	31.8 (\pm 7.8)	30.4 (\pm 8.3)	31.9 (\pm 9.5)	-1.3 (-7.0 to 4.4)	0.1 (-7.7 to 7.9)
BF % (%)	37.5 (\pm 5.2)	34.4 (\pm 6.2)	35.6 (\pm 5.3)	-3.1 (-9.0 to 2.9)	-1.9 (-10.3 to 6.6)

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457 Data presented as mean (\pm SD). RTR = Renal Transplant Recipients; NDD-CKD = Non-Dialysis Dependent Chronic Kidney Disease; DXA =
 458 Dual-energy X-ray Absorptiometry; BIA = Bioelectrical Impedance Analysis; LoA = Limits of Agreement taken from Bland-Altman plots; BF %
 459 = Body Fat %

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464 **Table 3.** Intraclass correlation coefficient and regression correlation coefficient between DXA, BIA, and the Hume formula

	DXA vs BIA				DXA vs Hume formula			
	ICC (<i>r</i>)	ICC (95CI)	<i>r</i> ²	<i>P</i>	ICC (<i>r</i>)	ICC (95CI)	<i>r</i> ²	<i>P</i>
RTR (n = 35)								
Lean mass (kg)	.984 (excellent)	.969 to .992	0.99	<.001*	.960 (excellent)	.922 to .980	0.97	<.001*
Fat mass (kg)	.972 (excellent)	.944 to .986	0.97	<.001*	.960 (excellent)	.920 to .980	0.96	<.001*
BF % (%)	.954 (excellent)	.909 to .977	0.96	<.001*	.859 (good)	.720 to .929	0.89	<.001*
NDD-CKD (n = 26)								
Lean mass (kg)	.980 (excellent)	.955 to .991	0.98	<.001*	.950 (excellent)	.890 to .978	0.95	<.001*
Fat mass (kg)	.967 (excellent)	.926 to .985	0.97	<.001*	.947 (excellent)	.882 to .976	0.96	<.001*
BF % (%)	.927 (excellent)	.837 to .967	0.94	<.001*	.808 (good)	.571 to .914	0.82	<.001*

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466 Data presented as mean (±SD). ICC – Intraclass Correlation Coefficient (95CI = 95% Confidence Intervals); RTR = Renal Transplant Recipients;
467 NDD-CKD = Non-Dialysis Dependent Chronic Kidney Disease; DXA = Dual-energy X-ray Absorptiometry’ BIA = Bioelectrical Impedance
468 Analysis BF % = Body Fat %

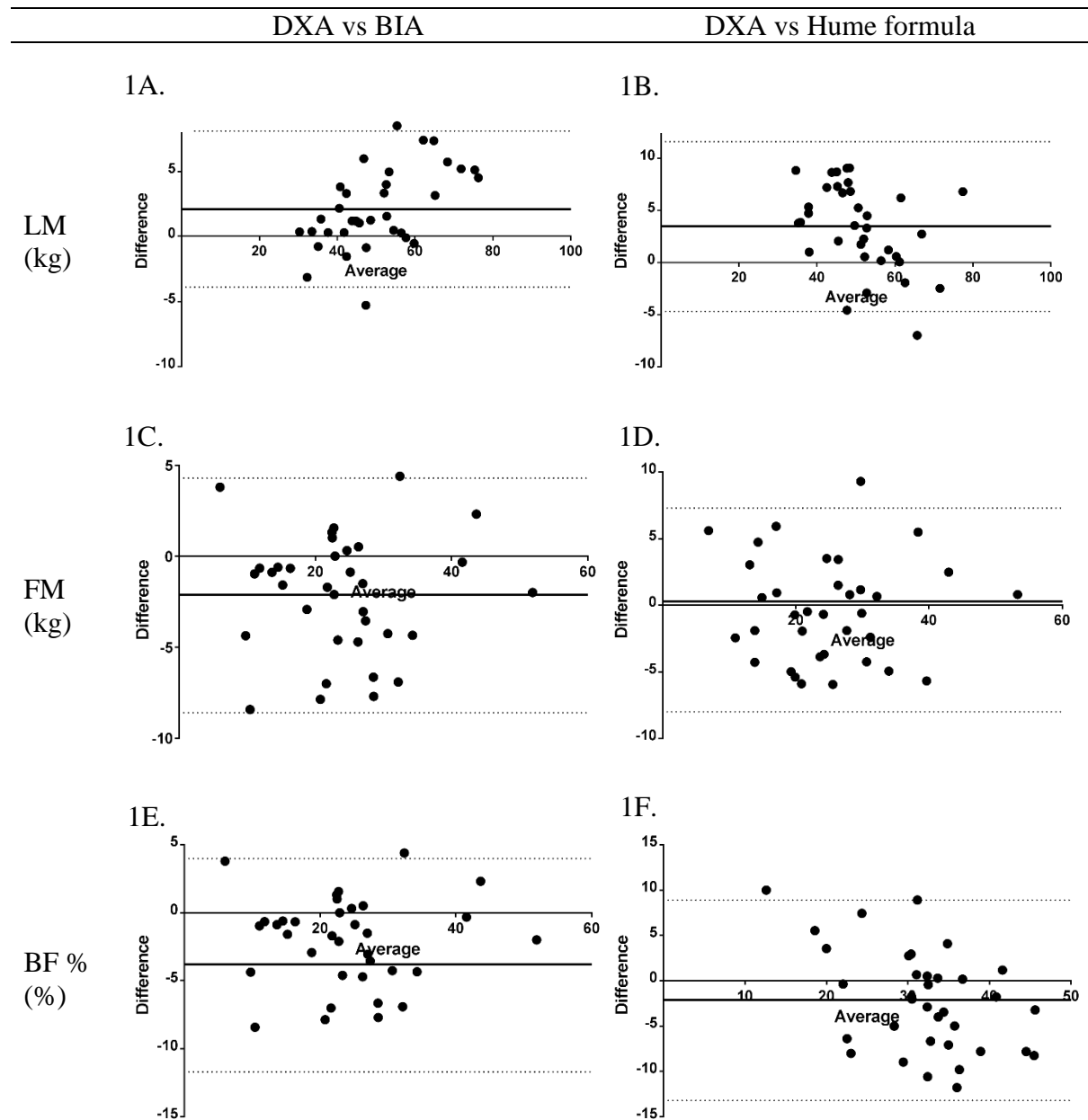
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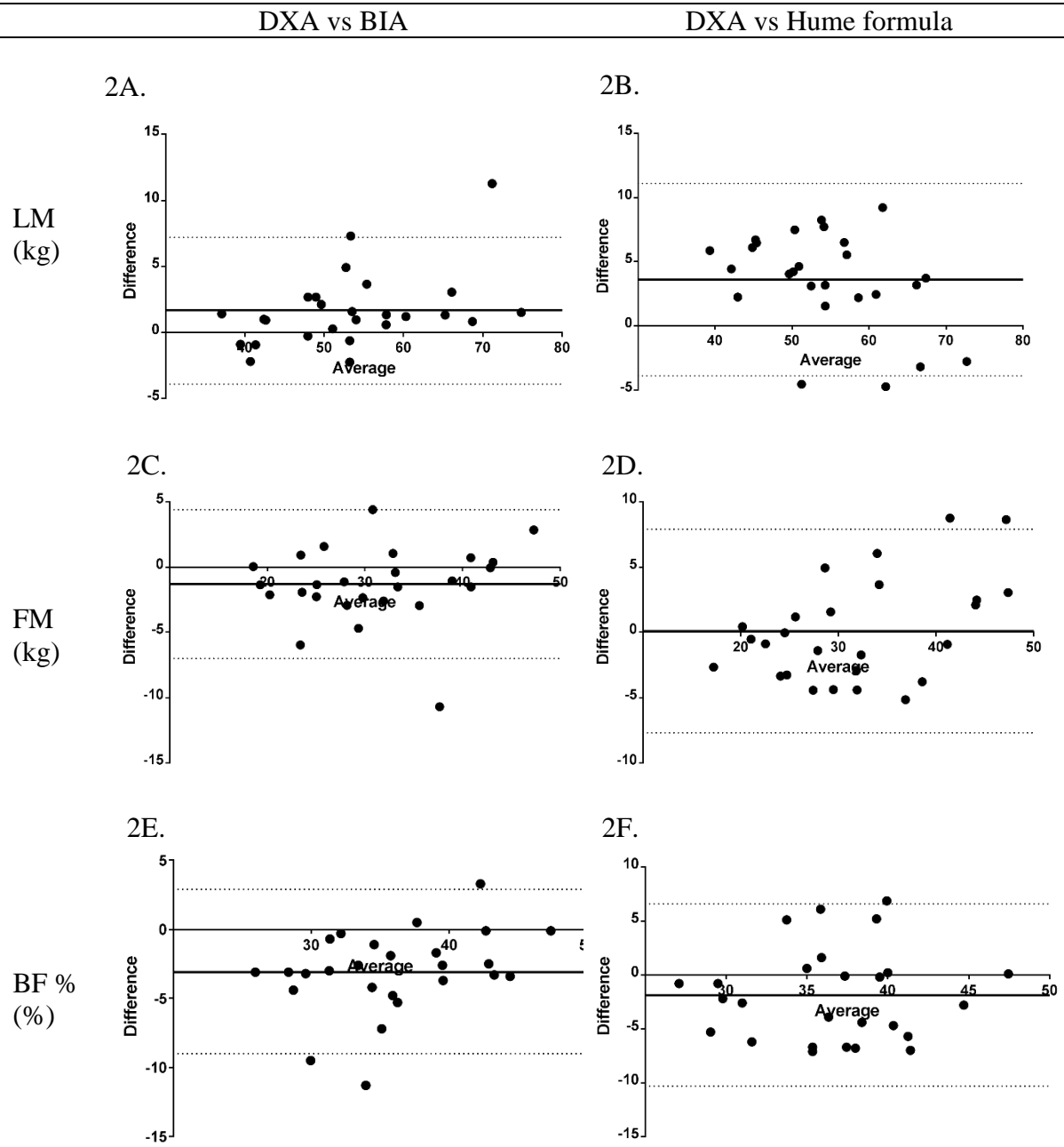
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Figure 1. Bland-Altman plots showing difference vs average for RTR



Bland-Altman plots show difference vs average. Dashed lines show upper and lower 95CI Limits of Agreement. Thick bold line shows mean bias. RTR = Renal Transplant Recipients; DXA = Dual-energy X-ray Absorptiometry; BIA = Bioelectrical Impedance Analysis; LM = Lean Mass; FM = Fat Mass; BF % = Body Fat %

Figure 2. Bland-Altman plots showing difference vs average for NDD-CKD



Bland-Altman plots show difference vs average. Dashed lines show upper and lower 95CI Limits of Agreement. Thick bold line shows mean bias. NDD-CKD = Non-Dialysis Dependent Chronic Kidney Disease; DXA = Dual-energy X-ray Absorptiometry; BIA = Bioelectrical Impedance Analysis; LM = Lean Mass; FM = Fat Mass; BF % = Body Fat %