BMC
Pharmacology & Toxicology

Lean body mass: the development and validation of prediction equations in healthy adults

Solomon Yu[1,2,3,6*], Thavarajah Visvanathan[4], John Field[3], Leigh C Ward[5], Ian Chapman[3], Robert Adams[6], Gary Wittert[3] and Renuka Visvanathan[1,2,3,6]

Abstract

Background: There is a loss of lean body mass (LBM) with increasing age. A low LBM has been associated with increased adverse effects from prescribed medications such as chemotherapy. Accurate assessment of LBM may allow for more accurate drug prescribing. The aims of this study were to develop new prediction equations (PEs) for LBM with anthropometric and biochemical variables from a development cohort and then validate the best performing PEs in validation cohorts.

Methods: PEs were developed in a cohort of 188 healthy subjects and then validated in a convenience cohort of 52 healthy subjects. The best performing anthropometric PE was then compared to published anthropometric PEs in an older (age ≥ 50 years) cohort of 2287 people. Best subset regression analysis was used to derive PEs. Correlation, Bland-Altman and Sheiner & Beal methods were used to validate and compare the PEs against dual X-ray absorptiometry (DXA)-derived LBM.

Results: The PE which included biochemistry variables performed only marginally better than the anthropometric PE. The anthropometric PE on average over-estimated LBM by 0.74 kg in the combined cohort. Across gender (male vs. female), body mass index (< 22, 22- < 27, 27- < 30 and ≥30 kg/m^2) and age groups (50–64, 65–79 and ≥80 years), the maximum mean over-estimation of the anthropometric PE was 1.36 kg.

Conclusions: A new anthropometric PE has been developed that offers an alternative for clinicians when access to DXA is limited. Further research is required to determine the clinical utility and if it will improve the safety of medication use.

Keywords: Lean body mass, Weight, Older people, Drugs

Background

With increasing age, there is a decline in lean body mass (LBM) and very often an increase in adiposity [1]. The decline in LBM may also be accompanied by a reduction in physical function and when a pathological threshold is reached, the person is said to have sarcopenia [2]. In recent times, sarcopenia has been recognized as an independent predictor of drug related adverse outcomes in the oncology setting where muscle wasting can be common [3,4]. Drug-related adverse effects are defined as

medical events related to the use of medication which may result in disability, hospital admissions or death [5]. In patients with cancer, the use of LBM might be superior to body surface area (BSA) [6]. For example, in a prospective study of colon cancer patients treated with 5-fluorouracil (5-FU), the incidence of dose limiting toxicity was examined with respect to conventional dosing of 5-FU/m^2 of BSA versus 5-FU/kg of LBM. LBM was a better predictor of toxicity (p = 0.011) but not BSA [6]. Similar findings have been reported in other studies [7,8]. In anaesthesia, propofol pharmacokinetic parameters scaled linearly to LBM is also said to provide for improved dosing in adults [9]. Therefore, accurate measurement of LBM may have clinical application in improving drug prescribing safety and efficacy, especially in older people where loss of lean mass is common.

* Correspondence: solomon.yu@adelaide.edu.au
[1]Aged and Extended Care Services, Level 8B Main Building, The Queen Elizabeth Hospital, Central Adelaide Local Health Network, 21 Woodville Road, 5011 Woodville South, SA, Australia
[2]Adelaide Geriatrics Training and Research with Aged Care (G-TRAC) Center, School of Medicine, University of Adelaide, South Australia, Australia
Full list of author information is available at the end of the article

A major impediment to the routine clinical use of LBM is the reliance on relatively inaccessible or expensive methods of body composition measurements. Computed tomography (CT), magnetic resonance imaging and dual absorptiometry x-ray (DXA) are used to assess LBM but these methods may be difficult to access in clinical practice (e.g. frail or rural patients) [10]. Although the bioelectrical impedance analysis (BIA) method is portable, it still requires the purchase of special equipment and it's accuracy is also dependent on many other factors such as state of hydration, food intake and exercise [11].

Total body weight consists of fat mass and fat free mass. Fat free mass (FFM) consists of bone, muscle, vital organs and extracellular fluid. LBM differs from FFM in that lipid in cellular membranes are included in LBM but this accounts for only a small fraction of total body weight (up to 3% in men and 5% in women) [12]. In the literature, bone mass has at times been included in LBM and at other times not included [4,13].

Anthropometric-based prediction equations (PEs) have been examined as an alternative in measuring LBM in settings where access to these accurate methods is limited. In a very recent study of older (≥70 years) Australian men, FFM as estimated by three PEs were compared to FFM as estimated by DXA (FFM_{DXA}) [14]. The three PEs were the Heitmann, Janmahasatian and Deurenberg equations as shown below:

Heitmann equation [15]:

$$Body\ fat\ (kg)_{male} = (0.988 \times BMI) \\ + (0.242 \times weight) \\ + (0.094 \times age) - 30.180$$

$$Body\ fat\ (kg)_{female} = (0.988 \times BMI) \\ + (0.344 \times weight) \\ + (0.094 \times age) - 30.180.$$

Janmahasatian equation [12]:

$$FFM\ (kg)_{female} = (9270 \times weight) \\ /(8780 + (244 \times BMI))$$

$$FFM\ (kg)_{male} = (9270 \times weight) \\ /(6680 + (216 \times BMI))$$

Deurenberg equation [16]:

$$Body\ fat(\%) = (1.2 \times BMI) \\ + (0.23 \times Age) - (10.8 \times Sex) - 5.4$$

Male = 1, Female = 0

For two of the PEs (Heitmann and Deurenberg equations), FFM was calculated by subtracting fat mass from total body mass. In defining the FFM and LBM, the authors in that study proposed that FFM and LBM could be used interchangeably. Mitchell et al. reported that FFM as estimated by Deurenberg equation had the smallest mean difference and overestimated FFM_{DXA} for overweight men but underestimated FFM_{DXA} for all other body mass index (BMI) subgroups [14]. The Heitmann and Janmahasatian equations, on the other hand, overestimated FFM_{DXA} across various BMI categories [14].

The addition of biochemistry variables might improve the performance of prediction equations but few studies have examined this. Creatine Kinase (CK) is found predominantly in skeletal muscle and serum levels were associated with the lean muscle mass [17]. There has only been one study evaluating the relationship between LBM and plasma creatine kinase activity (CK) and a weak and partial correlation ($r < 0.262$) between log CK and LBM was reported [18]. Serum albumin has also been reported to reflect protein reserve and lower albumin levels have been shown to be associated with loss of lean mass [19].

Therefore, the aims of this study were to develop and validate PEs for LBM with anthropometric and biochemistry variables against DXA.

Methods

The Central Northern Adelaide Health Service Ethics of Human Research Committee approved this study. All participants provided written informed consent.

Study cohorts

Four study cohorts were investigated in this study: a) the Cytokine, Adiposity, Sarcopenia and Ageing (CASA) cohort; b) the validation cohort (VC); c) the North West Adelaide Health Study (NWAHS) cohort and d) the Florey Adelaide Male Ageing Study (FAMAS) cohort. CASA was used to derive the PEs for LBM which included anthropometric and biochemistry variables. The selected LBM PEs were then validated in a second independent cohort, the VC (n = 52). As sarcopenia is more prevalent in older populations, validation of the best performing PE and other published FFM PEs (Heitmann, Janmahasatian and Deurenberg equations) were then undertaken in the larger population representative NWAHS and FAMAS cohorts (n = 2287, age ≥ 50 years).

CASA

195 population representative healthy subjects (age 18 to 83 years) were recruited from the western suburbs of Adelaide [20]. The inclusion criteria were: being aged 18 and above, able to comply with study protocol and weight stable over the last 3 months. We excluded those with a serious medical illness, an acute illness in the pass 3 months or in the 2 weeks following blood sampling, an inability to stop medications for 3 days prior to blood sampling, being in receipt of vaccinations and pregnancy. In undertaking the analysis, data from 7 subjects were excluded due to haemolysed or insufficient blood samples.

VC

This was a convenience sample of 52 healthy subjects (age 22 – 83 years) recruited through advertisement for another study [21]. Subjects with known medical illness including gastrointestinal disease or symptoms, significant respiratory, renal or cardiac disease and who were pregnant were excluded from this study.

NWAHS

This is a longitudinal study of community dwelling adults aged eighteen years and older. The population which is a representative biomedical cohort of predominantly of mixed European descent has been described in detail previously [22]. DXA scans were offered to NWAHS participants who were aged ≥ 50 years at follow up (median time = 4 years). Participants with complete anthropometric and DXA measurements at follow up (2004–06) aged ≥50 were included in this analysis (n = 1575).

FAMAS

This male only cohort has also been described in detail elsewhere [23]. The recruitment process was very similar to that used for the NWAHS and so the men in FAMAS were comparable with men in the same age groups from the NWAHS study and of mixed European descent [24]. DXA measurements at baseline (2002–2005) were obtained on 700 participants aged 50 years and over.

Measurements
Anthropometry

Height (m) was measured without shoes using a wall-mounted SECA stadiometer to the nearest 0.1 cm. Weight (kg) was measured wearing light clothing to the nearest 0.1 kg (A&D FV platform scales 0.5 – 150 kg). Body mass index (BMI, weight/height^2) was calculated. The healthy BMI for older people is said to be between 22–27 kg/m^2 [25]. Caucasians with BMI > 30 kg/m^2 were classified as obese [26].

Dual Energy X-ray Absorptiometry (DXA)

DXA analysis in all cohorts measured 3 compartments of the total body composition; fat mass, LBM and bone mineral content. For the purpose of this study, LBM refers to soft tissues and muscle mass, but excludes fat and bone mass. CASA: A Lunar PRODIGY whole-body scanner (GE Medical Systems, Madison, WI), in conjunction with Encore 2002 software, was used to estimate LBM. The majority of subjects underwent DXA within 2 hours of attending the morning clinic when blood sampling occurred. VC: A Norland densitometer XR36 (Norland Medical Systems, Fort Atkinson, Wisconsin, USA), in conjunction with Illuminatus 4.2.4a software, was used to estimate LBM. The DXA was performed on a separate study

day but within 2 weeks of blood sampling and given that the subjects were healthy, it is unlikely that there would have been significant change in body composition within that time frame. To account for differences between machines, LBM data from the VC had a correction factor applied to convert the data to Lunar equivalent [27]. NWAHS and FAMAS: The fan-beam Lunar PRODIGY (GE Medical Systems, Madison, WI) in conjunction with Encore 2002 software and a pencil-beam DPX + (GE Medical Systems, Madison, WI) in conjunction with LUNAR software version 4.7e were used. Cross-calibration analysis had been undertaken and no differences between these 2 densitometers were reported [28].

Blood analyses

For both the CASA and VC cohorts, a venous sample was obtained from each participant after an overnight fast. Both cohorts were asked to refrain from smoking, consuming alcohol or vigorous exercise in the 24 hours before the clinic appointment. Last regular medications were taken the day before and the morning dose was held until after venous sampling. For CASA, the blood was placed in ethylenediaminetetraacetic acid (EDTA) tubes and transported immediately to the Institute for Medical and Veterinary Sciences Laboratories (IMVS) in South Australia for analysis. The blood was centrifuged at 5000 rpm for 7 minutes and analyzed immediately at 37°C. For the VC, samples that had been centrifuged and stored at −70°C were transferred to be processed by the IMVS using the same methodology. The measured co-efficients of variation (CV) were: alanine transferase (ALT, 1.98%), aspartate transaminase (AST, 2.8%),albumin (2.8%), creatinine (3%), lactate dehydrogenase (LDH, 2.2%), creatinine kinase (CK, 2.2%) and high sensitivity C-reactive protein (hsCRP, 1.4%). A Beckman Coulter AU 2700 was used to perform the blood analysis and the methods, reagents and calibration were as per manufacturer instructions.

Statistical analysis

Demographic characteristics in both groups were expressed as mean ± standard deviation (SD). Independent samples t test was used to compare means between the two cohorts. Differences between methods of LBM measurements in the same cohort were examined by paired t test. PEs for LBM were developed from CASA where the independent variable was DXA derived LBM. The initial 10 independent variables were gender, age, weight, height, body mass index, albumin, AST, LDH, CK and hsCRP. The best PEs (as assessed by adjusted R^2: the proportion of the variance of the dependent variable accounted for by the independent variables, and adjusted for the number of independent variables) were developed considering up to 6 equations with n predictors.

For each *n*, the PE for validation was selected by considering the adjusted R^2 value and likely clinical utility. In the VC, LBM was calculated from the developed prediction equations (LBM_{PE}) and compared with DXA derived LBM (LBM_{DXA}).

The anthropometric PE was also compared to other known PEs [12,15,16] in the NWAHS and FAMAS cohorts.

To assess the accuracy and predictive performance of the prediction equations against LBM_{DXA}, a regression analysis as proposed by Lin [29] was undertaken and the concordance correlation coefficient (ρ_c) was derived. ρ_c measures how much the data deviates from the line of identity representing congruence between the methods. It is a product of Pearson correlation (ρ) and bias correction factor (C_b): $\rho_c = \rho \, C_b$ [30].

In addition, to assess the level of agreement between the two methods, Bland-Altman analysis was performed to obtain the 95% limits of agreement [31]. Furthermore, the goodness of fit with root mean square error (RMSE) and bias (mean error [ME]) was also determined. RMSE and ME were calculated according to the method of Sheiner and Beal [32]. When the 95% confidence interval of the ME includes 0 (i.e. no error), it indicates that the model is not biased. In this study, mean difference was taken to be the same as ME. This gives an estimation of R^2 and the standard error of the estimate [SEE]. SPSS 11.5 for Windows software (SPSS, Inc., Chicago, IL) and the R statistical language (R Foundation for Statistical Computing, Vienna, Austria) were used for the analyses. $P < 0.05$ was considered statistically significant.

Results

The CASA and VC cohorts were similar in age (CASA mean [SD] 49.2 [17.0] vs. VC 50.6 [15.7] years), but younger than the NWAHS (64.7 [9.84] years) and FAMAS (62.3 [8.2] years) cohorts. The BMI (23.7 [2.3] vs. 26.7 [5.2] kg/m^2) and CK (93.3 [54.7] vs. 114.3 [66.0] U/L), were significantly lower in the VC compared to the CASA. LDH (194.4 [37.8] vs. 175.0 [37.4] U/L) and albumin (40.4 [2.5] vs. 39.1 [3.1] g/L) were significantly higher in the VC compared to the CASA. No significant differences between the two cohorts were noted for hsCRP or LBM. The BMI of subjects in the NWAHS and FAMAS studies were higher at 28.2 [4.8] and 28.6 [4.6] kg/m^2 respectively.

Based on adjusted R^2 and potential clinical utility, the following PEs were selected for further validation in the VC:

Table 1 compares LBM_{PE1-4} to LBM_{DXA} in the VC. LBM predicted by all PEs was highly correlated with LBM_{DXA}. Concordance correlations, a measure of the degree to which the data lie on the line of identity, were all around 0.9 and similar to the Pearsons correlation coefficient. All PEs over-estimated LBM_{DXA}, ranging from 1.9% for PE$_1$ to 4.1% for PE$_4$. The limits of agreement were similar for all PEs, approximately ± 15%. With increasing number of variables, there were reducing RMSE and mean error indicating improving precision and reducing bias. Because of the costs involved with blood investigations and the marginal benefits, only the anthropometric PE$_1$ was selected for further comparison in the combined NWAHS and FAMAS cohorts (Tables 2, 3 and 4). Furthermore, biochemistry was not readily available from those cohorts.

Table 2 compares the performance of various PEs including PE$_1$ against LBM_{DXA} in the total combined NWAHS and FAMAS cohorts as well as in the two gender groups, men and women. All PEs over-estimated the LBM_{DXA} in the total group. PE$_1$ demonstrated a lower mean error and RMSE score than the Heitmann and Janmahasatian equations in the total population, men and women cohorts. The Deurenberg equation performed the best in the total population with the lowest mean error and RMSE. However, when reviewed within gender groups, PE$_1$ performed better than the Deurenberg equation in women where both equations over-estimated LBM. In men, the Deurenberg equation under-estimated LBM whilst all other equations over-estimated LBM.

Table 3 compares the performance of the various PEs across age groups (60–64, 65–79, ≥80). PE$_1$ consistently over-estimated LBM_{DXA} across the age groups but performed better (lowest ME, RMSE values and higher concordance correlation coefficient) than the Janmahasatian and Heitmann equations. The Deurenberg equation did not perform as well as PE$_1$ in the 50- < 65 years age group and the ≥ 80 years age group and over-estimated LBM in the 50- < 65 years age group but under-estimated LBM in the other two age groups.

Table 4 compares the performance of the various PEs across various BMI groups. Once again, PE$_1$ has the smallest ME and RMSE compared with the Janmahasatian and Heitmann equations across all the BMI groups analyzed but all of these consistently over-estimated LBM_{DXA} across the various BMI groups. PE$_1$, in comparison with the Deurenberg equation has a lower ME and RMSE in the obese BMI (>30 kg/m^2) and underweight BMI

$$LBM_{PE1} = 22.93 + 0.68(weight) - 1.14(BMI) - 0.01(age) + 9.94(if\ male)\ SEE = 3.61, R^2 = 90.7$$
$$LBM_{PE2} = 22.06 + 0.67(weight) - 1.11(BMI) + 9.76(if\ male) + 0.01(CK)\ SEE = 3.56, R^2 = 91.0$$
$$LBM_{PE3} = 21.19 + 0.67(weight) - 1.04(BMI) + 9.51(if\ male) - 0.56(CRP) + 0.01(CK)\ SEE = 3.47, R^2 = 91.4$$
$$LBM_{PE4} = 23.17 + 0.64(weight) - 0.91(BMI) + 9.45(if\ male) + 0.02(CK) - 0.58(CRP) - 0.02(LDH)\ SEE = 3.38, R^2 = 91.9$$

Table 1 Validation of PE LBM in healthy adults from the Cytokine, Adiposity, Sarcopenia and Ageing (CASA) study cohort (n = 195) against DXA derived LBM in the validation cohort (n = 52)

	Mean (SD), kg	Mean error (95%CI), kg	P-value for mean error	R	ρ_c (95% CI) [C_b]	95% limits of agreement	RMSE (95% CI), kg
Total (n = 52)							
LBM$_{DXA}$	46.2 (9.49)						
LBM$_{PE1}$	48.1 (8.93)	1.88 (0.79, 2.97)	0.001	0.911*	0.891 (0.820, 0.935) [0.977]	−9.72, 5.96 (−20.7 to 12.6%)	4.32 (2.84, 5.80)
LBM$_{PE2}$	47.9 (8.95)	1.69 (0.62, 2.75)	0.003	0.915*	0.899 (0.832, 0.940) [0.982]	−9.20, 5.83 (−19.9 to 12.6%)	4.15 (2.70, 5.60)
LBM$_{PE3}$	47.7 (9.13)	1.50 (0.44 ,2.57)	0.006	0.917*	0.904 (0.840, 0.943) [0.986]	−8.99, 5.98 (−19.5 to 13.0%)	4.07 (2.63, 5.51)
LBM$_{PE4}$	47.1 (8.96)	0.86 (−0.22, 1.94)	0.114	0.914*	0.908 (0.846, 0.946) [0.994]	−8.44, 6.72 (−18.3 to 14.6%)	3.93 (2.51, 5.35)

*P-value <0.001, R = correlation, SD = Standard Deviation.
RMSE = root mean squared prediction error, CI = confidence interval, R = Pearson Correlation Coefficient, C_b = Bias Correction Factor, ρ_c = Concordance Correlation Coefficient.

(< 22 kg/m^2) groups. Interestingly, the Deurenberg equation has less bias and better precision than PE$_1$ in predicting LBM$_{DXA}$ in the 22-27 kg/m^2 BMI group. The Deurenberg equation overestimated LBM$_{DXA}$ except in the underweight and obese categories.

Discussion

In this study, prediction equations for LBM were developed and validated. It was hypothesized that the addition of biochemistry variables would result in an improvement in the performance of the PEs and this was seen.

However, the improvement was marginal and insufficient to justify the additional costs.

A significant finding from this study wasthe development of a new anthropometric PE (PE$_1$) for LBM: *LBM = 22.932326 + 0.684668 (weight) -1.137156 (BMI) -0.009213 (age) + 9.940015 (if male).* The close approximation to LBM$_{DXA}$ generated by this equation was reflected by its small bias (ME = 0.74 kg) and precision (RMSE = 3.73 kg). It overestimated LBM$_{DXA}$ across gender, age and BMI groups. This PE may be useful in care settings where access to DXA may be limited, providing clinicians a

Table 2 Performance of the CASA (LBM$_{PE1}$) and previously published FFM prediction equations in the NWAHS and FAMAS cohorts (age 50 years and over) in the combined cohort and by gender

	Mean (SD), kg	Mean error (95%CI), kg	P-value for mean error	R	ρ_c (95% CI) [C_b]	95% limits of agreement	RMSE (95% CI), kg
Total (n = 2287)							
LBM$_{DXA}$	50.62 (10.8)						
Heitmann equation	54.30 (10.7)	3.68 (3.53, 3.83)	<0.001	0.940*	0.888 (0.880, 0.896) [0.945]	−3.77, 11.1	5.24 (4.97, 5.51)
Janmahasatian equation	54.23 (11.0)	3.61 (3.46, 3.76)	<0.001	0.943*	0.884 (0.884, 0.899) [0.946]	−3.78, 11.0	5.17 (4.90, 5.44)
Deurenberg equation	50.64 (10.1)	0.02 (−0.14, 0.19)	0.777	0.931*	0.928 (0.923, 0.934) [0.998]	−7.89, 7.93	3.95 (3.70, 4.20)
LBM$_{PE1}$	51.36 (10.6)	0.74 (0.59, 0.89)	<0.001	0.942*	0.939 (0.934, 0.944) [0.998]	−6.58, 8.06	3.73 (2.48, 4.98)
Men (n = 1436)							
LBM$_{DXA}$	57.09 (7.50)						
Heitmann equation	60.56 (7.80)	3.46 (3.25. 3.67)	<0.001	0.863*	0.782 (0.764, 0.800) [0.906]	−11.5, 4.57	5.30 (4.93, 5.67)
Janmahasatian equation	61.18 (6.80)	4.09 (3.89, 4.29)	<0.001	0.852*	0.728 (0.707, 0.747) [0.853]	−12.0, 3.82	5.69 (5.32, 6.06)
Deurenberg equation	56.76 (6.80)	- 0.34 (−0.55, -0.12)	0.002	0.838*	0.834 (0.818, 0.848) [0.995]	−7.92, 8.60	4.14 (3.85, 4.43)
LBM$_{PE1}$	58.22 (6.11)	1.12 (0.92, 1.33)	<0.001	0.851*	0.822 (0.806, 0.837) [0.851]	−6.78, 9.02	4.11 (3.80, 4.42)
Women (n = 851)							
LBM$_{DXA}$	39.70 (5.30)						
Heitmann equation	43.74 (5.55)	4.04 (3.83, 4.26)	<0.001	0.833*	0.651 (0.620, 0.680) [0.782]	−10.3, 2.26	5.12 (4.75, 5.49)
Janmahasatian equation	42.50 (5.39)	2.81 (2.60, 3.01)	<0.001	0.837*	0.722 (0.693, 0.749) [0.872]	−8.91, 3.29	4.14 (3.83, 4.45)
Deurenberg equation	40.32 (4.90)	0.63 (0.39, 0.87)	<0.001	0.759*	0.751 (0.721, 0.779) [0.990]	−7.75, 6.49	3.61 (3.29, 3.93)
LBM$_{PE1}$	39.78 (5.11)	0.08 (−0.12, 0.28)	0.433	0.835*	0.835 (0.813, 0.854) [0.999]	−5.91, 6.07	2.99 (2.74, 3.24)

Mean Error = DXA-PE; LBM, Lean Body Mass; DXA, Dual X-ray absorptiometry; RMSE, Root Mean Square Error; CI, Confidence interval; SD, Standard Deviation; R, Pearson Correlation; C_b = Bias Correction Factor; ρ_c = Concordance Correlation Coefficient; *p-value <0.001.

Table 3 Performance of the CASA (LBM$_{PE1}$) and previously published FFM prediction equations in the NWAHS and FAMAS cohorts (age 50 years and over) across various age groupings

	Mean (SD), kg	Mean error (95%CI), kg	P-value for mean error	R	ρ_c (95% CI) [C_b]	95% limits of agreement	RMSE (95% CI), kg
Age 50–64, years (n = 1265)							
LBM$_{DXA}$	52.27 (11.2)						
Heitmann equation	56.47 (10.8)	4.20 (3.99, 4.40)	<0.001	0.944*	0.879 (0.868, 0.890) [0.932]	−11.6, 3.23	5.60 (5.26, 5.95)
Janmahasatian equation	55.62 (11.2)	3.35 (3.15, 3.55)	<0.001	0.948*	0.907 (0.897, 0.915) [0.956]	−10.6, 3.85	4.92 (4.61, 5.23)
Deurenberg equation	53.15 (10.0)	0.87 (0.66, 1.09)	<0.001	0.938*	0.929 (0.921, 0.936) [0.990]	−8.72, 6.98	4.02 (3.73, 4.31)
LBM$_{PE1}$	52.77 (10.7)	0.50 (0.30, 0.70)	<0.001	0.948*	0.946 (0.939, 0.951) [0.998]	−6.68, 7.68	3.62 (3.36, 3.88)
Age 65–79, years (n = 882)							
LBM$_{DXA}$	49.09 (9.91)						
Heitmann equation	52.23 (10.0)	3.14 (2.90, 3.38)	<0.001	0.933*	0.887 (0.873, 0.899) [0.951]	−10.5, 4.18	4.82 (4.35, 5.29)
Janmahasatian equation	53.03 (10.5)	3.93 (3.69, 4.18)	<0.001	0.933*	0.862 (0.846, 0.876) [0.925]	−11.5, 3.66	5.46 (4.97, 5.95)
Deurenberg equation	48.19 (9.14)	−0.90 (−1.15, -0.65)	<0.001	0.924*	0.916 (0.905, 0.926) [0.993]	−6.70, 8.50	3.90 (3.45, 4.35)
LBM$_{PE1}$	50.20 (10.2)	0.98 (0.73, 1.22)	<0.001	0.929*	0.925 (0.915, 0.934) [0.995]	−6.57, 8.53	3.90 (3.48, 4.32)
Age ≥80, years (n = 140)							
LBM$_{DXA}$	44.48 (8.64)						
Heitmann equation	46.71 (9.20)	2.23 (1.60, 2.85)	<0.001	0.929*	0.902 (0.868, 0.928) [0.969]	−9.05, 4.59	4.06 (3.20, 4.92)
Janmahasatian equation	48.46 (10.1)	3.97 (3.29, 4.66)	<0.001	0.936*	0.850 (0.806, 0.883) [0.906]	−11.4, 3.46	5.43 (4.31, 6.55)
Deurenberg equation	42.46 (8.41)	−2.03 (−2.58, -1.48)	<0.001	0.937*	0.911 (0.880, 0.934) [0.971]	−3.97, 8.03	3.61 (2.85, 4.37)
LBM$_{PE1}$	45.84 (9.81)	1.36 (0.80, 1.93)	<0.001	0.941*	0.923 (0.897, 0.943) [0.981]	−5.39, 8.11	3.63 (2.90, 4.36)

Mean Error = DXA-PE; LBM, Lean Body Mass; DXA, Dual X-ray absorptiometry; RMSE, Root Mean Square Error; CI, Confidence interval; SD, Standard Deviation; R, Pearson Correlation; C_b = Bias Correction Factor; ρ_c = Concordance Correlation Coefficient; *p-value <0.001.

practical alternative to assess LBM. Furthermore, it also provides a bedside option in hospitals for ill and frail patients where transport for DXA assessment may be difficult. Whilst BIA may be simple technique to be used at the beside, BIA may be affected by clinical factors such as ascites, hydration status, food intake and exercise and cannot be used in older people with pacemakers [11]. Skin fold measurements may be a cheaper option but the accuracy is operator dependent and the loss of subcutaneous tissue in older people may also affect accuracy [33].

Interestingly, the Deurenberg equation appeared to have less bias with a ME of 0.02 kg but similar precision with a RMSE of 3.95 when compared to the newly developed PE. However, across gender, age and BMI groups, it at times over-estimated and at other times underestimated the LBM$_{DXA}$ [14]. The newly developed PE$_1$ appeared to have better precision (smaller RMSE) and less bias (lower ME) than the Deurenberg equation only in women and in obese older individuals. In clinical settings where the dose normalization to LBM is required, an overestimation of LBM could potentially lead to higher incidence of dose limiting toxicity. Sarcopenia was an important predictor of toxicity in women with metastatic cancer and colon cancer receiving chemotherapy [4,6]. It was suggested that chemotherapy dose normalization to LBM may reduce the excess toxicity in women. PE$_1$ in our study potentially offers a more accurate estimation of LBM over Deurenberg equation in women and obese individuals and may have clinical utility in this two patient population groups.

This study had several limitations. Only 6% of the study population was under-weight with a BMI < 22 kg/m^2 and therefore, it remains important to validate this newly developed PE in an under-weight population where sarcopenia is likely to be common. Furthermore, only Caucasians were studied and therefore generalizing these results to other ethnic communities is not possible and ethnic specific PEs will need to be developed. Different DXA machines were used in the CASA and VC cohort studies. This may have affected the results as even in the same person, reported measurements of the same tissue mass can be different with different DXA machines [34]. The researchers adjusted for the difference between the machines in the validation aspects of this study but clearly, it would have been preferable to use the same DXA machine in both cohorts. The use of other anthropometry measurements such as calf or arm circumference may improve the performance of prediction equations and needs to be explored in future studies.

Table 4 Performance of the CASA (LBM$_{PE1}$) and previously published FFM prediction equations in the NWAHS and FAMAS cohorts (age 50 years and over) across various body mass index groupings

	Mean (SD), kg	Mean error (95%CI), kg	P-value for mean error	R	ρ_c (95% CI) [C$_b$]	95% limits of agreement	RMSE (95% CI), kg
BMI < 22 kg/m^2 (n = 135)							
LBM$_{DXA}$	42.45 (8.85)						
Heitmann equation	44.85 (7.65)	2.40 (1.85, 2.96)	<0.001	0.932*	0.885 (0.847, 0.914) [0.949]	−4.12, 8.92	4.04 (3.21, 4.87)
Janmahasatian equation	43.72 (9.26)	1.27 (0.77, 1.77)	<0.001	0.946*	0.937 (0.914, 0.955) [0.989]	−4.65, 7.19	3.21 (2.55, 3.87)
Deurenberg equation	41.26 (8.04)	−1.18 (−1.77, -0.60)	<0.001	0.921*	0.909 (0.876, 0.933) [0.986]	−8.04, 5.68	3.62 (2.86, 4.36)
LBM$_{PE1}$	43.52 (9.04)	1.08 (0.57, 1.59)	<0.001	0.944*	0.937 (0.913, 0.955) [0.993]	−4.92, 7.08	3.18 (2.53, 3.83)
BMI 22- < 27 kg/m^2 (n = 847)							
LBM$_{DXA}$	47.45 (9.18)						
Heitmann equation	50.67 (8.67)	3.22 (2.99, 3.44)	<0.001	0.933*	0.874 (0.860, 0.888) [0.938]	−3.42, 9.86	4.62 (4.26,4.98)
Janmahasatian equation	50.81 (9.71)	3.36 (3.13, 3.59)	<0.001	0.937*	0.880 (0.866, 0.893) [0.939]	−3.41, 10.1	4.77 (4.39, 5.15)
Deurenberg equation	47.91 (8.68)	0.45 (0.22, 0.68)	0.001	0.928*	0.925 (0.915, 0.934) [0.997]	−6.42, 7.32	3.46 (3.16, 3.76)
LBM$_{PE1}$	48.64 (9.45)	1.19 (0.96, 1.41)	<0.001	0.938*	0.930 (0.920, 0.938) [0.992]	−5.41, 7.79	3.51 (3.20, 3.82)
BMI 27- < 30 kg/m^2 (n = 596)							
LBM$_{DXA}$	52.00 (9.83)						
Heitmann equation	55.65 (9.48)	3.65 (3.36, 3.95)	<0.001	0.929*	0.867 (0.847, 0.883) [0.933]	−3.65, 10.9	5.16 (4.69, 5.63)
Janmahasatian equation	56.11 (9.75)	4.12 (3.83, 4.41)	<0.001	0.932*	0.857 (0.837, 0.874) [0.919]	−3.08, 11.3	5.47 (4.97, 5.97)
Deurenberg equation	52.58 (9.23)	0.59 (0.30, 0.88)	<0.001	0.928*	0.925 (0.912, 0.935) [0.996]	−6.72, 7.90	3.70 (3.35, 4.05)
LBM$_{PE1}$	52.80 (9.69)	0.81 (0.52, 1.09)	<0.001	0.933*	0.929 (0.918, 0.939) [0.997]	−6.37, 7.99	3.67 (3.31, 4.03)
BMI ≥30 kg/m^2 (n = 709)							
LBM$_{DXA}$	54.80 (11.7)						
Heitmann equation	59.30 (11.7)	4.50 (4.19, 4.80)	<0.001	0.937*	0.867 (0.847, 0.883) [0.933]	−3.80, 12.8	6.12 (5.53, 6.71)
Janmahasatian equation	58.93 (11.0)	4.13 (3.83, 4.43)	<0.001	0.937*	0.857 (0.837, 0.974) [0.919]	−4.02, 12.3	5.80 (5.22, 6.38)
Deurenberg equation	54.07 (10.6)	−0.74 (−1.08, -0.39)	<0.001	0.917*	0.925 (0.912, 0.935) [0.996]	−10.0, 8.55	4.70 (4.14, 5.26)
LBM$_{PE1}$	54.88 (11.3)	0.08 (−0.23, 0.38)	0.628	0.936*	0.929 (0.918, 0.939) [0.997]	−8.15, 8.31	4.11 (3.61, 4.61)

Mean Error = DXA-PE; LBM, Lean Body Mass; DXA, Dual X-ray absorptiometry; RMSE, Root Mean Square Error; CI, Confidence interval; SD, Standard Deviation; R, Pearson Correlation; C$_b$ = Bias Correction Factor; ρ_c = Concordance Correlation Coefficient.
*p-value <0.001.

Conclusions

This study describes the development of a new prediction equation for LBM as estimated by DXA. This new PE consistently over-estimates across gender, age and BMI groups. There remains a need to confirm these findings in older and leaner cohorts, cohorts with diseases (e.g. renal failure), as well as other cohorts with varying ethnicity. The anthropometric PE is an alternative when access to DXA is difficult and this might occur with home bound frail older people as well as people residing in rural areas. The availability of simple and accuratemethods to estimate LBM might be the necessary catalyst required to support better prescribing to limit toxicity in the oncology setting.

Authors' contributions

RV, TV, RA and SY contributed to the initial study design. SY contributed to the data collection, data entry and statistical analysis. JF undertook the statistical analysis required to develop the PEs. LW performed the LBM data correction to adjust differences between dual x-ray absorptiometry machines in this study. All authors contributed to the interpretation of the analysis and preparation of this manuscript. All authors read and approved the final manuscript.

Author details

[1]Aged and Extended Care Services, Level 8B Main Building, The Queen Elizabeth Hospital, Central Adelaide Local Health Network, 21 Woodville Road, 5011 Woodville South, SA, Australia. [2]Adelaide Geriatrics Training and Research with Aged Care (G-TRAC) Center, School of Medicine, University of Adelaide, South Australia, Australia. [3]Discipline of Medicine, School of Medicine, Faculty of Health Science, University of Adelaide, Adelaide, SA, Australia. [4]Department of Anaesthesia, The Queen Elizabeth Hospital, Central Adelaide Local Health Network, South Australia, Australia. [5]School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, QLD, Australia. [6]The Health Observatory, Discipline of Medicine, School of Medicine, Faculty of Health Science, University of Adelaide, Adelaide, South Australia, Australia.

References

1. Visvanathan R, Chapman I: **Preventing sarcopaenia in older people.** *Maturitas* 2010, **66**(4):383–388.
2. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, et al: **Sarcopenia: european consensus on definition and diagnosis: report of the european working group on sarcopenia in older people.** *Age Ageing* 2010, **39**(4):412–423.
3. Parsons HA, Baracos VE, Dhillon N, Hong DS, Kurzrock R: **Body composition, symptoms, and survival in advanced cancer patients referred to a phase I service.** *PLoS One* 2012, **7**(1):e29330.
4. Prado CM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, Tonkin K, Mackey JR, Koski S, Pituskin E, Sawyer MB: **Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment.** *Clin Cancer Res* 2009, **15**(8):2920–2926.
5. Nebeker JR, Barach P, Samore MH: **Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting.** *Ann Intern Med* 2004, **140**(10):795–801.
6. Prado CM, Baracos VE, McCargar LJ, Mourtzakis M, Mulder KE, Reiman T, Butts CA, Scarfe AG, Sawyer MB: **Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity.** *Clin Cancer Res* 2007, **13**(11):3264–3268.
7. Gusella M, Toso S, Ferrazzi E, Ferrari M, Padrini R: **Relationships between body composition parameters and fluorouracil pharmacokinetics.** *Br J Clin Pharmacol* 2002, **54**(2):131–139.
8. Aslani A, Smith RC, Allen BJ, Pavlakis N, Levi JA: **The predictive value of body protein for chemotherapy-induced toxicity.** *Cancer* 2000, **88**(4):796–803.
9. Coetzee JF: **Allometric or lean body mass scaling of propofol pharmacokinetics: towards simplifying parameter sets for target-controlled infusions.** *Clin Pharmacokinet* 2012, **51**(3):137–145.
10. Heymsfield SB, Nunez C, Testolin C, Gallagher D: **Anthropometry and methods of body composition measurement for research and field application in the elderly.** *Eur J Clin Nutr* 2000, **54**(3):S26–32.
11. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gomez JM, Heitmann BL, Kent-Smith L, Melchior JC, Pirlich M, et al: **Bioelectrical impedance analysis–part I: review of principles and methods.** *Clin Nutr* 2004, **23**(5):1226–1243.
12. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B: **Quantification of lean bodyweight.** *Clin Pharmacokinet* 2005, **44**(10):1051–1065.
13. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE: **A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care.** *Appl Physiol Nutr Metab* 2008, **33**(5):997–1006.
14. Mitchell SJ, Kirkpatrick CM, Le Couteur DG, Naganathan V, Sambrook PN, Seibel MJ, Blyth FM, Waite LM, Handelsman DJ, Cumming RG, et al: **Estimation of lean body weight in older community-dwelling men.** *Br J Clin Pharmacol* 2010, **69**(2):118–127.
15. Heitmann BL: **Evaluation of body fat estimated from body mass index, skinfolds and impedance. A comparative study.** *Eur J Clin Nutr* 1990, **44**(11):831–837.
16. Deurenberg P, Weststrate JA, Seidell JC: **Body mass index as a measure of body fatness: age- and sex-specific prediction formulas.** *Br J Nutr* 1991, **65**(2):105–114.
17. Norton JP, Clarkson PM, Graves JE, Litchfield P, Kirwan J: **Serum creatine kinase activity and body composition in males and females.** *Hum Biol* 1985, **57**(4):591–598.
18. Swaminathan R, Ho CS, Donnan SP: **Body composition and plasma creatine kinase activity.** *Ann Clin Biochem* 1988, **25**(Pt 4):389–391.
19. Visser M, Kritchevsky SB, Newman AB, Goodpaster BH, Tylavsky FA, Nevitt MC, Harris TB: **Lower serum albumin concentration and change in muscle mass: the health, aging and body composition study.** *Am J Clin Nutr* 2005, **82**(3):531–537.
20. Dent E, YU S, Visvanathan R, Piantadosi C, Adams R, Lange K, Chapman I: **Inflammatory cytokines and appetite in healthy people.** *J Ageing Res Clin Pract* 2012, **1**(1):40–43.
21. Tai K, Visvanathan R, Hammond AJ, Wishart JM, Horowitz M, Chapman IM: **Fasting ghrelin is related to skeletal muscle mass in healthy adults.** *Eur J Nutr* 2009, **48**(3):176–183.
22. Grant JF, Taylor AW, Ruffin RE, Wilson DH, Phillips PJ, Adams RJ, Price K: **Cohort profile: the north west adelaide health study (NWAHS).** *Int J Epidemiol* 2009, **38**(6):1479–1486.
23. Martin S, Haren M, Taylor A, Middleton S, Wittert G: **Cohort profile: the florey adelaide male ageing study (FAMAS).** *Int J Epidemiol* 2007, **36** (2):302–306.
24. Grant JF, Chittleborough CR, Taylor AW, Dal Grande E, Wilson DH, Phillips PJ, Adams RJ, Cheek J, Price K, Gill T, et al: **The north west adelaide health study: detailed methods and baseline segmentation of a cohort for selected chronic diseases.** *Epidemiol Perspect Innov* 2006, **3**:4.
25. Visvanathan R: *Under-nutrition and Older People.* Position Statement No. 6, http://www.anzsgm.org/posstate.asp.
26. **Obesity: preventing and managing the global epidemic. Report of a WHO consultation.** *World Health Organ Tech Rep Ser* 2000, **894**(i-xii):1–253.
27. Maple-Brown LJ, Hughes J, Piers LS, Ward LC, Meerkin J, Eisman JA, Center JR, Pocock NA, Jerums G, O'Dea K: **Increased bone mineral density in aboriginal and torres strait islander australians: impact of body composition differences.** *Bone* 2012, **51**(1):123–130.
28. Mazess RB, Barden HS: **Evaluation of differences between fan-beam and pencil-beam densitometers.** *Calcif Tissue Int* 2000, **67**(4):291–296.
29. Lin LI: **A concordance correlation coefficient to evaluate reproducibility.** *Biometrics* 1989, **45**(1):255–268.
30. Chumlea WC, Baumgartner RN: **Status of anthropometry and body composition data in elderly subjects.** *Am J Clin Nutr* 1989, **50**(5 Suppl):1158–1166. discussion 1231–1155.
31. Bland JM, Altman DG: **Measuring agreement in method comparison studies.** *Stat Methods Med Res* 1999, **8**(2):135–160.
32. Sheiner LB, Beal SL: **Some suggestions for measuring predictive performance.** *J Pharmacokinet Biopharm* 1981, **9**(4):503–512.

33. Omran ML, Morley JE: **Assessment of protein energy malnutrition in older persons. Part II: laboratory evaluation.** *Nutrition* 2000, **16**(2):131–140.

34. Tothill P, Hannan WJ: **Comparisons between hologic QDR 1000W, QDR 4500A, and lunar expert dual-energy X-ray absorptiometry scanners used for measuring total body bone and soft tissue.** *Ann N Y Acad Sci* 2000, **904**:63–71.