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Quantification of Lean Bodyweight

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Abstract

Background: Lean bodyweight (LBW) has been recommended for scaling drug doses. However, the current methods for predicting LBW are inconsistent at extremes of size and could be misleading with respect to interpreting weight-based regimens.

Objective: The objective of the present study was to develop a semi-mechanistic model to predict fat-free mass (FFM) from subject characteristics in a population that includes extremes of size. FFM is considered to closely approximate LBW. There are several reference methods for assessing FFM, whereas there are no reference standards for LBW.

Patients and methods: A total of 373 patients (168 male, 205 female) were included in the study. These data arose from two populations. Population A (index dataset) contained anthropometric characteristics, FFM estimated by dual-energy x-ray absorptiometry (DXA – a reference method) and bioelectrical impedance analysis (BIA) data. Population B (test dataset) contained the same anthropometric measures and FFM data as population A, but excluded BIA data. The patients in population A had a wide range of age (18–82 years), bodyweight (40.7–216.5kg) and BMI values (17.1–69.9 kg/m^2). Patients in population B had BMI values of 18.7–38.4 kg/m^2. A two-stage semi-mechanistic model to predict FFM was developed from the demographics from population A. For stage 1 a model was developed to predict impedance and for stage 2 a model that incorporated predicted impedance was used to predict FFM. These two models were combined to provide an overall model to predict FFM from patient characteristics. The developed model for FFM was externally evaluated by predicting into population B.

Results: The semi-mechanistic model to predict impedance incorporated sex, height and bodyweight. The developed model provides a good predictor of impedance for both males and females ($r^2 = 0.78$, mean error [ME] = 2.30×10^{-3}, root mean square error [RMSE] = 51.56 [approximately 10% of mean]). The final model for FFM incorporated sex, height and bodyweight. The developed model

for FFM provided good predictive performance for both males and females (r^2 = 0.93, ME = −0.77, RMSE = 3.33 [approximately 6% of mean]). In addition, the model accurately predicted the FFM of subjects in population B (r^2 = 0.85, ME = −0.04, RMSE = 4.39 [approximately 7% of mean]).

Conclusions: A semi-mechanistic model has been developed to predict FFM (and therefore LBW) from easily accessible patient characteristics. This model has been prospectively evaluated and shown to have good predictive performance.

Background

Obesity is recognised as a serious medical and public health problem in both developed and developing countries,[1] and is a major risk factor for serious noncommunicable diseases such as diabetes mellitus and cardiovascular disease.[1] Unfortunately, dosage recommendations in drug labels are predominantly developed from clinical trials that exclude special patient populations such as the obese, or have not specifically quantified how body composition affects the exposure response relationship. Drug administration in clinical practice is therefore based on the premise that structural and functional aspects of the body are similar in obese and normal-weight patients, and can be scaled to total bodyweight, usually presented in the drug label as a dose per kilogram.

Selecting a drug dose that is scaled according to bodyweight is unlikely to result in comparable exposures between obese and nonobese patients. This arises as body composition usually varies as a function of total bodyweight, with the ratio of adipose tissue to lean body mass increasing with bodyweight.[2] Whilst bodyweight remains the most common size descriptor to scale drug dose, other descriptors such as lean bodyweight (LBW)[3] have been recommended for the drugs enoxaparin sodium,[4] amikacin[5] and suxamethonium chloride.[6] The most widely used equations to calculate LBW are shown in the format described by Green and Duffull[7] (equations 1 and 2):

$$\text{LBW (male)} = 1.10 \times \text{BWt} - 0.0128 \times \text{BMI} \times \text{BWt} \quad \text{(Eq. 1)}$$

$$\text{LBW (female)} = 1.07 \times \text{BWt} - 0.0148 \times \text{BMI} \times \text{BWt} \quad \text{(Eq. 2)}$$

where BWt is bodyweight and BMI is body mass index.

Some authors have suggested that LBW is likely to be a better predictor of drug dosage in the obese,[8] as good correlations between LBW and volume of distribution have been seen for hydrophilic drugs. The current estimate of LBW[3] is, however, inconsistent at extremes of size,[7] and could be misleading with respect to interpreting bodyweight-based regimens as normal-weighted patients have a normal amount of fat mass, which is ignored in computation of LBW. This has stimulated researchers to develop a new size descriptor termed 'predicted normal bodyweight' (PNWT), which can be used to predict normal bodyweight for individuals who are obese.[9] Nevertheless, PNWT itself relies on the current equation[3] to predict LBW, which will therefore necessarily confer the same prediction limitations seen with LBW. Refinement of the PNWT equation with a more accurate equation for predicting LBW is therefore required.

When considering human body composition, total bodyweight is believed to be comprised of fat mass and fat-free mass (FFM). FFM consists of muscle, bone, vital organs and extracellular fluid. Technically, LBW differs from FFM because lipids in cellular membranes, the CNS and bone marrow are included in LBW[10] but not in FFM. However, as lipid included with LBW is generally a small fraction of total bodyweight (approximately 3% in males and 5% in females), the terms FFM and LBW for the purposes of assessing body composition for drug administration can be considered interchangeable. Clinically, measuring body fat is difficult and no accurate method is available for routine clinical use.[11] Measurement of FFM is easier and common-

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ly performed using bioelectrical impedance analysis (BIA) or dual-energy x-ray absorptiometry (DXA).

Objective

The objective of this study was to develop a semi-mechanistic model for predicting FFM from subject characteristics. The study was conducted in two parts. The first part involved the development of a semi-mechanistic model for prediction of impedance from anthropometric measures. The second part incorporated a semi-mechanistic model to link the prediction of impedance from part 1 to estimates of FFM.

Bioelectrical Impedance Analysis (BIA)

BIA is a readily accessible method of assessing FFM. It is noninvasive, portable, inexpensive and provides immediate results. Although BIA is generally known as a method of measuring FFM, it actually estimates total body water. As water is a constant fraction of FFM (around 72% in males and 73% in females),[10] FFM can be estimated as the ratio of total body water to the constant water fraction. BIA measures the impedance or opposition of biological tissue to the flow of an alternating electric current. In the body, lean tissue preferentially conducts electricity since it contains water and electrolytes, while fat mass impedes the current flow as it is largely anhydrous. It can be readily shown that the measured impedance of a body is inversely related to total conductive volume (V) and to the length of the conductor (L). This relationship can be expressed as shown in equation 3:[12]

$$V = \rho L^2/R \quad \text{(Eq. 3)}$$

where ρ is the resistivity constant and R is the resistance. In practice, application of BIA theory to the human body is that the body is considered to be a single cylinder of length equal to stature height (Ht)[13] and the conductive volume is that of total body water (TBW) and is therefore proportional to the term Ht^2/R, which is termed the impedance index or quotient.[14] Impedance actually comprises two components, resistance and reactance. As the reactance is approximately 10% of the resistance,[12] and very small relative to impedance (<4%),[10] it is often assumed that resistance and impedance are approximately equivalent and are used interchangeably.[10,12,14] At present, a variety of equations have been presented in the literature to compute FFM from resistance or impedance, although it remains controversial as to which one is the most accurate and reliable.

Dual-Energy X-ray Absorptiometry (DXA)

DXA is regarded as a reference method for FFM estimation.[15] This method assumes that the body is comprised of three components, which can be distinguished by their x-ray attenuation properties. The three components are lean tissue mass, fat mass and bone mineral mass, and FFM is made up of lean tissue mass and bone mineral mass.[16] To measure body composition using DXA, two differing low-energy x-ray beams are passed through the body. Since the density of fat and lean tissues is different, the beams are attenuated to differing degrees. The attenuation ratio, which is the ratio of beam attenuation at the lower energy to higher energy, can then be applied to established mass attenuation equations[17] to estimate the mass of each component.

Patients and Methods

Patients

This study comprises data from two populations. Population A was comprised of 303 subjects (146 males and 157 females), of whom 88 (39 males and 49 females) were normal weight (BMI <25 kg/m^2) and 215 (107 males and 108 females) were overweight or obese (BMI ≥25 kg/m^2). The normal-weight subjects, including students and staff, were recruited from the University of Queensland, Brisbane, QLD, Australia. Approval for collection of these data was obtained from the Ethics Committee, School of Pharmacy, University of Queensland, Australia. All subjects gave informed consent to participate in the study. Both anthropometric and BIA data were recorded. Subjects who were (or

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could have been) pregnant were excluded, together with those who had medical electronic devices such as pacemakers. The data for overweight and obese subjects (BMI ≥25 kg/m^2) arose from two sites. Anthropometric measures and BIA data were available from a de-identified database of patients attending the Department of Diabetes and Endocrinology Obesity Clinic, at the Princess Alexandra Hospital, Brisbane, QLD, Australia, and were completed by one observer. This database was collected for clinical reasons. Anthropometric measures, BIA and DXA data were also provided from a BIA database maintained at the Department of Biochemistry and Molecular Biology, University of Queensland. Ethical approval was obtained for both datasets.

Population B was comprised of 70 subjects (22 males and 48 females), of whom 24 (4 males and 20 females) were normal weight (BMI <25 kg/m^2) and 46 (18 males and 28 females) were overweight or obese (BMI ≥25 kg/m^2). This population was obtained from body composition studies being undertaken at the School of Human Movement Studies, Queensland University of Technology, Brisbane, QLD, Australia, under ethics approval from the institution's Human Research Ethics Committee. This population contained the same anthropometric data and FFM data as population A but excluded BIA data.

Anthropometric Measurements

Height (cm), bodyweight (kg), waist circumference (cm) and hip circumference (cm) were measured. Height was measured to the nearest 1mm using a stadiometer, and bodyweight was measured to 0.1kg using digital scales. BMI was calculated as bodyweight (kg) divided by the square of height (m^2). Waist and hip circumference were measured with a tape measure. The waist-to-hip circumference ratio was calculated as waist circumference (cm) divided by hip circumference (cm).

BIA

Impedance was measured using a conventional tetrapolar technique while subjects were in a supine position. Electrodes that provided alternating current were placed at the base of the fingers and toes, with voltage sensing electrodes placed on the wrist and ankle at the mid-line between the bony prominences. Subjects were asked to empty their bladders before the measurement and not to take strenuous exercise 12 hours before the measurements. BIA instruments from different manufacturers were used at the different sites: a Bodystat 1500 (Bodystat Ltd, Douglas, Isle of Man, UK) single frequency (50 kHz) instrument was used at Princess Alexandra Hospital, and an SEAC SFB3 multifrequency instrument (Impedimed Pty Ltd, Brisbane, QLD, Australia) was used at the University of Queensland and Queensland University of Technology. All measurements were performed in accordance with the manufacturer's manual. In the case of the SFB3 multifrequency instrument, impedance data at 50 kHz only were used, comparable with that of the Bodystat instrument. Measurements performed with reference resistors showed that there was no difference between the two instruments.

DXA

Whole-body and regional (trunk, arm and leg) lean and fat tissue were determined with the use of DXA (DPX-L, Lunar Radiation Corp., Madison, WI, USA). The scans were analysed with the use of ADULT software, version 1.33 (Lunar Radiation Corp., Madison, WI, USA). The calculation of appendicular lean and fat mass was made according to the approach described by Heymsfield et al.[18] With the use of specific anatomic landmarks, the legs and arms are isolated on the skeletal x-ray planogram (anterior view). The arm encompasses all soft tissue extending from the centre of the arm socket to the phalange tips, and contact with the ribs, pelvis or greater trochanter is avoided. The leg consists of all soft tissue extending from an angled line drawn through the femoral neck to the phalange tips. The system software provides the total mass, ratio of soft tissue attenuations, and bone mineral mass for the isolated regions. The ratio of soft tissue attenuation for each region was used to divide bone mineral-free tissue of the extremities into fat and lean components. Limb fat and lean tissue were calculated from summed arm and leg fat, and lean tissues, respectively.

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Model Development

This study used impedance rather than resistance to develop a new model for predicting FFM. Two responses were available for model development – impedance and DXA-estimated FFM. These two responses were modelled sequentially, anthropomorphic measures to impedance and impedance to FFM, in order to provide a basis for development of two semi-mechanistic models. These models can ultimately be applied individually (if impedance is available clinically) or as a combined full model to predict FFM from patient anthropomorphic characteristics. The two responses were also modelled empirically, therefore providing four models for development:

1. an empirical model to describe impedance from anthropometric features;
2. a semi-mechanistic model to predict impedance from anthropomorphic features;
3. an empirical model to predict FFM from anthropometric features;
4. a semi-mechanistic model to predict FFM from impedance.

Both empirical models were developed using a data-driven approach, whereas the semi-mechanistic models were developed based on biological knowledge of the interactions between variables.

The empirical models were allowed to include up to ten anthropometric measures with second level interaction terms. The empirical models were used to represent a saturated model, i.e. the best possible model to describe the data, and were not intended for routine clinical use. The intended use of the saturated model was to determine the predictive loss associated with assuming *a priori* the functional relationships inherent in the semi-mechanistic models.

The empirical models to predict BIA (model 1) and FFM (model 3) from anthropometric data were developed using the statistical program NCSS 2001 and PASS Trial (Number Cruncher Statistical Systems, Kaysville, UT, USA). The semi-mechanistic model for BIA (model 2) was developed using MATLAB student version 6.5 (The MathWorks, Inc., San Diego, CA, USA). Finally, the semi-mechanistic model to describe FFM from impedance (model 4) was developed using NONMEM version 5 (Globomax, Hanover, MD, USA).[19]

Model Performance

The predictive performance of all models was assessed in terms of the mean error (ME) and root mean square error (RMSE).[20] ME is a measure of bias in prediction and the 95% confidence interval should include zero for a nonbiased model. RMSE is a measure of the precision of the model predictions. The predictive loss is presented as a ratio of the mean squared error of the semi-mechanistic model over the saturated model. Interpretation is intended to be considered only in terms of the fractional loss and not to have any specific statistical qualities. Finally, the semi-mechanistic FFM model was evaluated against an independent population (population B). The predictive performance in terms of ME and RMSE was computed.

Model 1: Empirical Model for Impedance

The empirical model was derived through stepwise multiple regression of population A. The dependent variable was the impedance measurement from the BIA, and the explanatory variables were the subjects' anthropometric measures. The best empirical model was selected using the Akaike Information Criterion (AIC),[21] which is a measure of the difference between goodness-of-fit and model complexity. The model with the smallest AIC is considered the model with the best overall statistical properties and parameter balance.

Model 2: Semi-Mechanistic Model for Impedance

The semi-mechanistic model was developed based on the assumption that the body is described as various cylindrical conductors (arms, legs and torso), and resistance for each cylindrical conductor is proportional to length (L) and inversely proportional to cross-sectional area (A). Resistance (R) also depends on the composition of the cylinder. This relationship can be shown by the following equation (equation 4):

$$R \propto L/A \times \text{composition} \quad \text{(Eq. 4)}$$

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In BIA, the resistive component is considered to dominate the impedance, as discussed in the background section, and overall cylindrical length is approximated as height; therefore, impedance (Z) can be expressed as equation 5:

$$Z \propto Ht/A \times \text{composition} \quad \text{(Eq. 5)}$$

In this approximation we assume that the composition of the body is similar between obese and nonobese subjects. As the body consists of fat mass and FFM, and we propose impedance is proportional to the concentration of fat mass, therefore (equation 6):

$$Z \propto Ht/A \times [\text{fat mass}] \quad \text{(Eq. 6)}$$

An indicator of the concentration of fat mass may be gained by considering the density of the body, since fat mass has lower density than FFM. If we assume that the composition of the body is uniform then it would seem reasonable to propose the relationship shown in equation 7:

$$Z \propto Ht/A \times \text{density}^{-1} \quad \text{(Eq. 7)}$$

Since density = bodyweight/body volume, and if we approximate body volume = $A \times Ht$, then (equations 8, 9 and 10):

$$Z \propto Ht/A \times [BWt/(A \times Ht)]^{-1} \quad \text{(Eq. 8)}$$

$$Z \propto Ht \times [BWt/Ht)]^{-1} \quad \text{(Eq. 9)}$$

$$Z \propto Ht^2/BWt \quad \text{(Eq. 10)}$$

As $BMI = BWt/Ht^2$, thus (equation 11):

$$Z \propto 1/BMI \quad \text{(Eq. 11)}$$

Finally, a regression model is proposed such that (equation 12):

$$Z = \theta_1/BMI + \theta_2 \quad \text{(Eq. 12)}$$

where θ_1 and θ_2 are parameters to be estimated in the model that may vary between males and females.

The semi-mechanistic model was developed based on population A using a cross-validation technique. In cross-validation, the population was split into two groups by random sampling without replacement. The first group comprised 90% of the total subjects and was used to estimate the model parameters, and the second group, comprising 10% of the total subjects, was used to evaluate the predictive performance of the developed model. This process was repeated 5000-fold to provide parameter estimates.

Model 3: Empirical Model to Predict Fat-Free Mass (FFM)

The empirical model was developed using stepwise multiple regression analysis, and the best model was again selected using the AIC.[21]

Model 4: Semi-Mechanistic Model to Predict FFM

Model 4 was a semi-mechanistic model that incorporated the prediction for impedance (from model 2) into a widely accepted model to predict FFM from BIA data.[22] This model takes the general form shown in equation 13:

$$FFM \propto Ht^2/\hat{Z} \quad \text{(Eq. 13)}$$

where $\hat{Z}$ is the predicted impedance.

Although the exact nature of the BIA index appears to have been empirically derived, it is biologically reasonable that FFM is inversely proportional to impedance but proportional to body size. On the basis of this relationship, the model to predict FFM from height and our predicted impedance is given as shown in equation 14:

$$FFM = \theta_3 \frac{Ht^{\theta_4}}{\hat{Z}^{\theta_5}} \quad \text{(Eq. 14)}$$

The effect of sex on the model used to predict FFM was also investigated, by allowing the parameter values (θ_1, θ_2, θ_3, θ_4, θ_5) to vary between males and females. Standard goodness-of-fit criteria, such as assessment of the objective function and parameter estimates, and diagnostic plots were assessed.

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Table I. Anthropometric, bioelectrical impedance analysis and dual-energy x-ray absorptiometry characteristics of study populations[a]

Parameter	Male		Female	
	population A (n = 146)	population B (n = 22)	population A (n = 157)	population B (n = 48)
Age (y)	18–82 (41 ± 11.7)	29–64 (49 ± 9.3)	19–79 (40 ± 12.0)	21–62 (45 ± 10.5)
Height (cm)	159.0–208.9 (177.5 ± 7.8)	159.0–189.0 (177 ± 8.0)	137.8–185.0 (164.0 ± 7.0)	151.0–187.0 (165.0 ± 6.0)
Bodyweight (kg)	60.6–216.5 (108.4 ± 34.6)	63.8–131.7 (90.3 ± 15.3)	40.7–196.2 (93.5 ± 33.7)	47.6–105.9 (71.4 ± 14.7)
Body mass index (kg/m^2)	18.2–69.9 (34.5 ± 11.0)	22.4–37.7 (28.6 ± 3.7)	17.1–66.3 (34.7 ± 12.3)	18.7–38.4 (26.2 ± 5.0)
Waist circumference (cm)	73.0–174.0 (111.5 ± 27.1)	82.0–116.5 (97.9 ± 9.8)	61.0–171.0 (100.0 ± 27.3)	63.0–111.0 (81.0 ± 12.3)
Hip circumference (cm)	88.0–184.0 (116.4 ± 21.0)	92.0–122.0 (105.7 ± 7.06)	82.0–187.0 (121.5 ± 25.0)	84.0–133.0 (105.3 ±11.0)
Waist-to-hip ratio	0.79–1.22 (0.95 ± 0.09)	0.80–1.06 (0.93 ± 0.07)	0.65–1.03 (0.81 ± 0.08)	0.69–0.95 (0.77 ± 0.06)
Impedance (ohm)	262.0–631.0 (428.9 ± 76.4)	NA	325.0–862.0 (529.9 ± 113.9)	NA
Fat-free mass (kg)	44.8–106.3 (72.2 ± 12.0)	40.7–78.8 (61.2 ± 8.7)	28.1–79.7 (50.5 ± 9.9)	34.4–73.8 (44.4 ± 5.6)

a Values are expressed as range (mean ± SD).

NA = not available.

Between-subject variance (BSV) for each parameter was also estimated. Goodness-of-fit was assessed by the objective function value of NONMEM and standard diagnostic plots. A statistically significant improvement in model fit was based on a drop in the objective function value of >3.84 units between two nested models ($\alpha = 0.05$, degrees of freedom = 1, χ^2).

Ultimately, models 4 and 2 would be combined to provide a single model for predicting FFM from patient characteristics. The developed model for FFM was externally evaluated by predicting into population B.

Results

A total of 373 subjects (168 males and 205 females) were studied. The anthropometric and BIA characteristics for each population are shown in table I. The data used to develop the model to predict impedance comprised of patient bodyweights that ranged from 40.7–216.5kg and BMI that ranged from 17.1–69.9 kg/m^2.

Development of Models to Predict Impedance

Model 1: Empirical Model for Impedance

The empirical (saturated) model that best predicted impedance was found to be a function of sex, bodyweight, age, waist size, height and hip size, and was described by the following equation 15:

$$\hat{Z} = 521 + (200 \times sex) - (10.1 \times bodyweight) - (8.23 \times age) + (3.17 \times waist) - (1.05 \times waist \times sex) + (4.31 \times age \times height) + (92.8 \times height^2) + (0.019 \times bodyweight^2) + (0.010 \times hip^2) \quad \text{(Eq. 15)}$$

where height is measured in metres, bodyweight is in kilograms, waist circumference is in centimetres, hip circumference is in centimetres and sex is coded as 0 for males and 1 for females. The predictive performance for the developed empirical model is shown in table II.

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Table II. The predictive performance of the empirical model for impedance

Sex	r^2	Mean error (95% CI)	Mean square error (95% CI)	Root mean square error (95% CI)
Male	0.73	−1.94 (−9.78, 5.89)	1.81×10^3 (1.05×10^3, 2.57×10^3)	42.5 (32.4, 50.7)
Female	0.79	5.81 (−3.84, 15.4)	3.12×10^3 (2.23×10^3, 4.01×10^3)	55.9 (47.2, 63.3)
Combined	0.82	2.16 (−4.15, 8.47)	2.50×10^3 (1.91×10^3, 3.10×10^3)	50.0 (43.7, 55.7)

Model 2: Semi-Mechanistic Model for Impedance

A reasonably strong relationship was found between impedance and the inverse of BMI. The association was found to be different between males and females (r^2 = 0.54 and 0.64, respectively) and is shown in figure 1. The equations for predicting impedance from BMI are given for males (equation 16) and females (equation 17):

$$\hat{Z}\,(\text{male}) = \frac{6.68 \times 10^3}{\text{BMI}} + 216 \qquad \text{(Eq. 16)}$$

$$\hat{Z}\,(\text{female}) = \frac{8.78 \times 10^3}{\text{BMI}} + 244 \qquad \text{(Eq. 17)}$$

Table III summarises the cross-validation results and the predictive performance for the semi-mechanistic models. The semi-mechanistic models incorporated bodyweight and height as a metric of BMI, while the empirical model incorporated bodyweight, height, age and waist and hip circumference. From the plot of predicted impedance versus measured impedance (figure 2), it is seen that the semi-mechanistic model for impedance provides a good predictor of the impedance for both males and females (r^2 = 0.67 and 0.74, respectively). There was no apparent bias for the semi-mechanistic model. The apparent loss in predictive performance was approximately 6%, where the ratio of the MSE for the semi-mechanistic model over the saturated empirical model for both sexes combined was 1.06. This appears to be an acceptably small loss of information associated with the biologically more plausible and simpler semi-mechanistic model. The absolute size of the precision (RMSE) was approximately 10% of the average value of impedance.

Model 3: Empirical Model to Predict FFM

The best empirical model to predict FFM was found to be (equation 18):

$$\text{FFM} = (1.59 \times \text{bodyweight}) - (0.087 \times \text{hip} \times \text{sex}) - (0.003 \times \text{hip} \times \text{waist}) - (0.004 \times \text{bodyweight}^2) - 16.2 \qquad \text{(Eq. 18)}$$

where bodyweight is in kilograms, hip circumference is in centimetres, waist circumference is in centimetres and sex is coded as 0 for males and 1 for females. The predictive performance for the developed empirical model is shown in table IV.

Model 4: Semi-Mechanistic Model to Predict FFM

Based on the BIA index Ht^2/Z hypothesis, the general predictive model for FFM (equation 14) generated using NONMEM was found to be (equation 19):

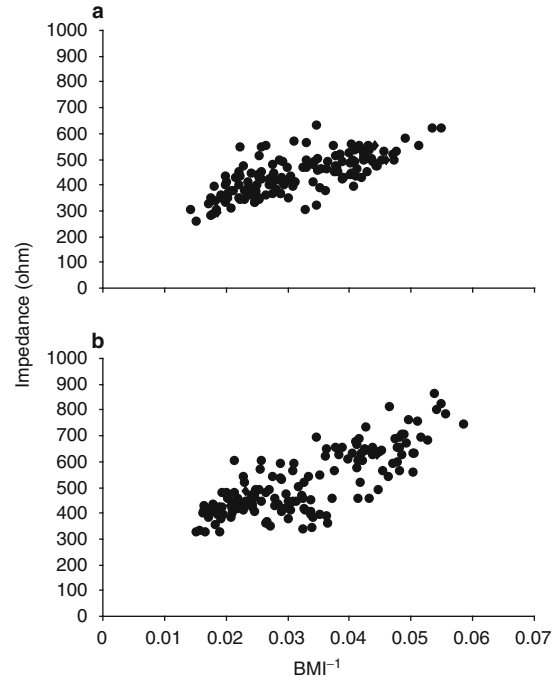

Fig. 1. Relationship between impedance and the inverse of body mass index (BMI) in (**a**) males and (**b**) females.

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Table III. Semi-mechanistic models for impedance developed using cross-validation technique

Sex	Model	SD of the slope	SD of the intercept	r^2	Mean error (95% CI)	Mean square error (95% CI)	Root mean square error (95% CI)
Male	$\hat{Z}\,(\text{male}) = \frac{6.68 \times 10^3}{BMI} + 216$	117.99	3.96	0.67	-1.62×10^{-2} (−7.08, 7.05)	1.89×10^3 (1.32×10^3, 2.46×10^3)	43.4 (36.3, 49.6)
Female	$\hat{Z}\,(\text{female}) = \frac{8.78 \times 10^3}{BMI} + 244$	146.55	4.44	0.74	1.96×10^{-2} (−9.10, 9.14)	3.38×10^3 (2.49×10^3, 4.26×10^3)	58.1 (49.9, 65.3)
Combined		NA	NA	0.78	2.30×10^{-3} (−5.81, 5.82)	2.66×10^3 (2.12×10^3, 3.20×10^3)	51.6 (46.0, 56.6)

BMI = body mass index; **NA** = not applicable; **SD** = standard deviation; $\hat{Z}$ = predicted impedance.

$$FFM = 9.27 \times 10^3 \times \frac{Ht(m)^2}{\hat{Z}} \quad \text{(Eq. 19)}$$

where θ_3 is 9.27×10^3, θ_4 was fixed at 2.00, and θ_5 was fixed at 1. Estimating θ_4 did not improve the fit of the model and the estimated value was 1.7. Fixing the value to 1.7 or 2.0 yielded the same objective function value from NONMEM, therefore the value of 2 was chosen. Estimating θ_5 yielded a value that was 0.922 and no improvement in model fit. This value was then fixed to 1.0. BSV was only able to be estimated for θ_3, and the variability between patients was found to be negligible (coefficient of variation = 0.27%). No statistical interaction was found between sex and any of the BIA index parameters. As shown in figure 3, the new model correlated well with the FFM measured by DXA with ME = −0.01 (95% CI −0.24, 0.22), RMSE = 1.07 (95% CI 0.90, 1.22) for FFM measured by DXA versus each individual's value of predicted FFM. The plots between residual and weighted residual versus model predictions from the new model against predicted population FFM are shown in figure 4. It can be seen that there was no evidence of bias in the model prediction.

The loss of information associated with the choice of a semi-mechanistic model, compared with the saturated empirical model, was 35%. This is higher than for the loss associated with the impedance model (6%). Estimation of the parameters θ_4 and θ_5 for the BIA index did not reveal a different relationship for this population, which adds credence to the model. The actual value of RMSE for the model was 3.3, which is only 6% of the average FFM estimated by DXA. This level of imprecision is of limited clinical concern.

Model to Predict FFM from Patient Characteristics

When the semi-mechanistic model for $\hat{Z}$ and FFM (from $\hat{Z}$), corresponding to models 2 and 4, were combined and simplified, the final model is shown in equations 20 and 21.

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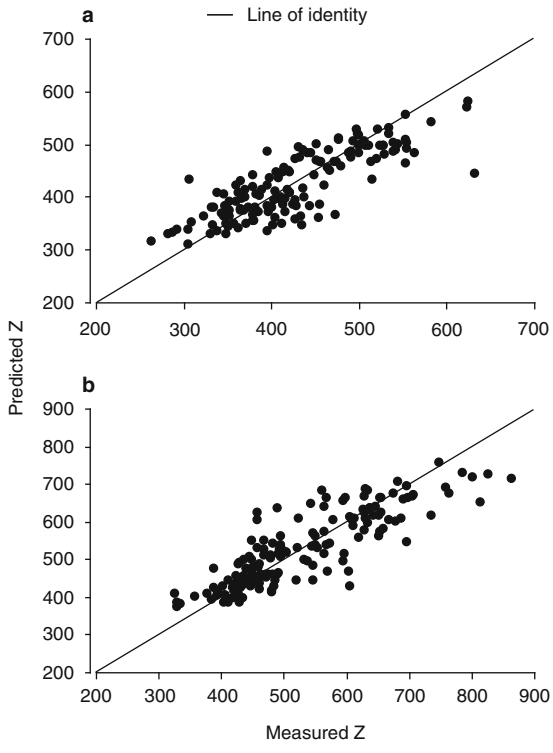

Fig. 2. Plot of predicted vs measured impedance (Z) for (**a**) males and (**b**) females.

$$\text{FFM (male)} = \frac{9.27 \times 10^3 \times \text{BWt}}{6.68 \times 10^3 + 216 \times \text{BMI}} \quad \text{(Eq. 20)}$$

$$\text{FFM (female)} = \frac{9.27 \times 10^3 \times \text{BWt}}{8.78 \times 10^3 + 244 \times \text{BMI}} \quad \text{(Eq. 21)}$$

Table IV shows the FFM predictive performance for the developed semi-mechanistic model.

The new model for FFM (equations 20 and 21) was used to predict FFM from population B, from subject characteristics in this population. The predicted FFM was plotted versus their observed value of FFM (from DXA) [figure 5]. Table V shows the predictive performance for the final model for FFM when used to predict FFM for subjects in population B. It can be seen that the new developed model to predict FFM from subject characteristics is not biased and the value of RMSE is approximately 7.3% that of the average value for FFM. In addition, when the model is applied to a typical range of heights and bodyweights, it concords well with the current equation for LBW.[3] Importantly, however, the estimate of LBW does not decline as bodyweight increases, nor does it lead to computation of a negative value of LBW at extremes of BMI (figure 6).

Discussion

This study reports on the development of a semi-mechanistic model for predicting FFM from the individual characteristics of patients. Demographics of the patients used to develop the model spanned a wide range of bodyweights (from 40.7 to 216.5kg) and BMI values (from 17.1 to 69.9 kg/m^2). It should be noted that 71% of the study patients were overweight or obese. Although this study involved the development of a predictive equation for FFM, in the clinical setting it is reasonable for FFM and LBW to be considered as equivalent descriptors, and hence this equation could be used to predict LBW. FFM differs from LBW in that FFM describes the

Table IV. The predictive performance of the model for fat-free mass

Model	r^2	Mean error (95% CI)	Mean square error (95% CI)	Root mean square error (95% CI)
Empirical model				
Male	0.82	−0.71 (−1.74, 0.33)	8.27 (3.86, 12.7)	2.88 (1.96, 3.56)
Female	0.81	−0.72 (−1.72, 0.32)	8.82 (4.33, 13.1)	2.97 (2.08, 3.62)
Combined	0.95	−0.73 (−1.45, −0.01)	8.25 (5.16, 11.4)	2.87 (2.27, 3.38)
Semi-mechanistic model				
Male	0.75	−1.27 (−2.49, −0.06)	12.4 (5.11, 19.7)	3.52 (2.26, 4.44)
Female	0.76	−0.28 (−1.43, 0.88)	9.79 (5.21, 14.4)	3.13 (2.28, 3.79)
Combined	0.93	−0.77 (−1.62, 0.07)	11.1 (6.82, 15.4)	3.33 (2.61, 3.92)

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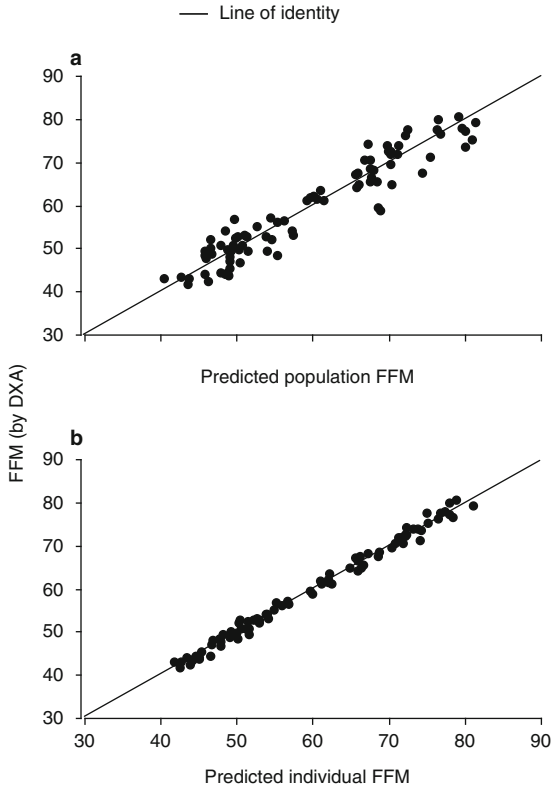

Fig. 3. Plot of fat-free mass (FFM) measured by dual-energy x-ray absorptiometry (DXA) vs (**a**) predicted population FFM and (**b**) predicted individual FFM calculated using the developed model for FFM.

mass of the body after excluding all fat content, whereas LBW is the mass of the body excluding fat content other than the lipids in cellular membranes, the CNS and bone marrow.[10] Nevertheless, lipid included within the descriptor LBW is a small fraction of total bodyweight (3% in males and 5% in females). The terms FFM and LBW are therefore used interchangeably.[23]

LBW is often used as a size descriptor to scale drug dose.[2] The equation currently used for LBW (see Cheymol[3] for details) was derived based on the study of James,[24] which included 133 patients from three studies.[25-27] The purpose of the James report was to provide a size descriptor that could be linked to mortality data for life insurance tables. This has provided a convenient application in the area of drug administration for patients who are obese; however, the study was not designed for this purpose and hence may have inherent limitations when extrapolated to this application. Recently, it has been suggested that the Cheymol/James equation for LBW leads to inconsistencies in the estimation of LBW at extremes of bodyweight and height. These inconsistencies lead to estimation of lower values of LBW at extremes of bodyweight than would seem reasonable and in some circumstances even lead to computation of negative values of LBW.[7] These inconsistencies are most likely due to the empirical nature of the evaluation of LBW as the difference between bodyweight and fat bodyweight (FBW), but where the predictor of FBW was based on a population where <10% of the study subjects were obese. Clearly, the population in the James study differs from the population demographics of today.

FFM is another size descriptor presented in the pharmacokinetic literature. Of the current work undertaken in this area, the simpler methods available

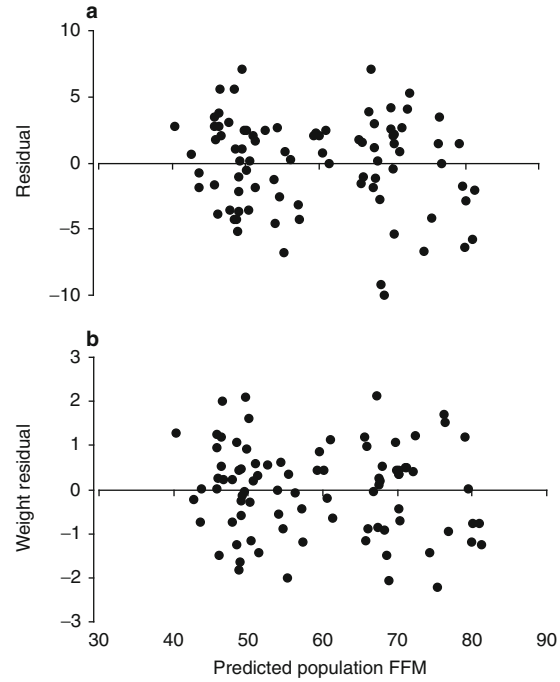

Fig. 4. Relationship between (**a**) residual and (**b**) weight residual from the developed model for fat-free mass (FFM) plotted against predicted population FFM.

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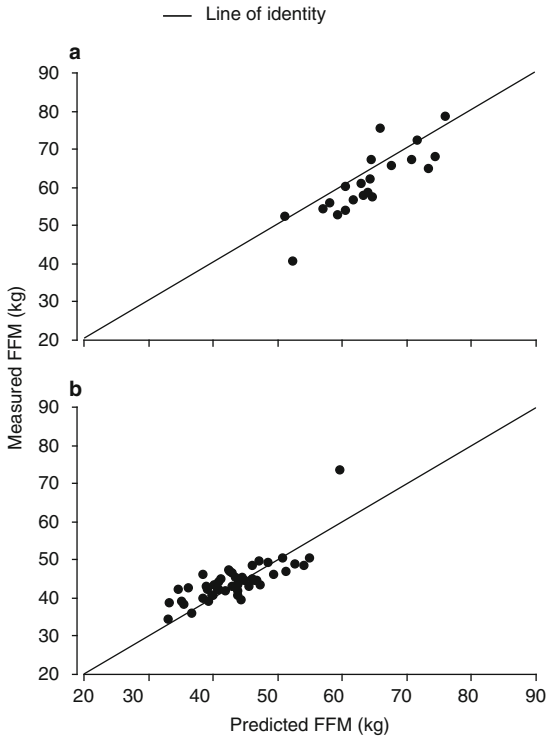

Fig. 5. Plot of predicted fat-free mass (FFM) using the new developed model vs FFM measured using dual-energy x-ray absorptiometry (population B) for (**a**) males and (**b**) females.

for estimation of FFM are BMI, skinfold thickness measurements and BIA. BMI or 'Quetelet's index' is widely used to classify obesity and is easy to perform.[28] To date, several equations for predicting body fat percentage from BMI have been developed[29,30] and FFM can be calculated as the difference between bodyweight and body fat. However, these equations were not developed from the population with a wide range of bodyweight.

Skinfold thickness measurement is one of the reliable methods for evaluating adiposity.[31] It has been reported that skinfold thickness measurements are better predictors of body fat percentage than BMI.[32,33] Nevertheless, skinfold thickness measurements require a considerable amount of technical skill in order to obtain accurate results. Additionally, skinfold thickness measurements cannot be performed in some obese patients because of the inadequate size of the calipers.[34] Although prediction equations to estimate FFM from skinfold thickness measurements have been published, it is likely that such equations are age, sex and population specific, which may lead to biased estimates of FFM when the equations are applied to a different population.

BIA is considered the most accurate of the 'simple' methods for estimation of FFM; however, the accuracy of BIA depends on the parameters and structure of the regression equation that links impedance with FFM.[35] To date, a variety of regression equations to predict FFM for BIA have been developed. Unfortunately, no well validated equation has been developed from obese subjects, which may lead to inconsistencies in prediction when these equations are extrapolated to an obese population. In addition, the clinical applicability of an equation that relies on an actual BIA measurement will be limited owing to the requirement for validated BIA equipment at all clinical locations. Hence, an accurate method that relies only on easily measured subject characteristics (e.g. bodyweight, height and sex) would be of significant clinical value.

The development of the semi-mechanistic model for predicting FFM from patient demographics in this study was conducted in two parts. The first part was to develop a semi-mechanistic model to predict impedance from subject characteristics, and the second part was to incorporate the semi-mechanistic model for impedance into an overall model to predict FFM. We use the term semi-mechanistic to

Table V. The predictive performance of the semi-mechanistic model for fat-free mass (FFM) when used to predict FFM for subjects in population B

Sex	r^2	Mean error (95% CI)	Mean square error (95% CI)	Root mean square error (95% CI)
Male	0.72	−2.74 (−4.76, −0.73)	28.6 (13.6, 43.7)	5.35 (3.69, 6.61)
Female	0.61	1.14 (0.07, 2.20)	15.2 (6.51, 23.8)	3.90 (2.55, 4.88)
Combined	0.85	−0.04 (−1.09, 1.00)	19.3 (11.6, 26.9)	4.39 (3.41, 5.19)

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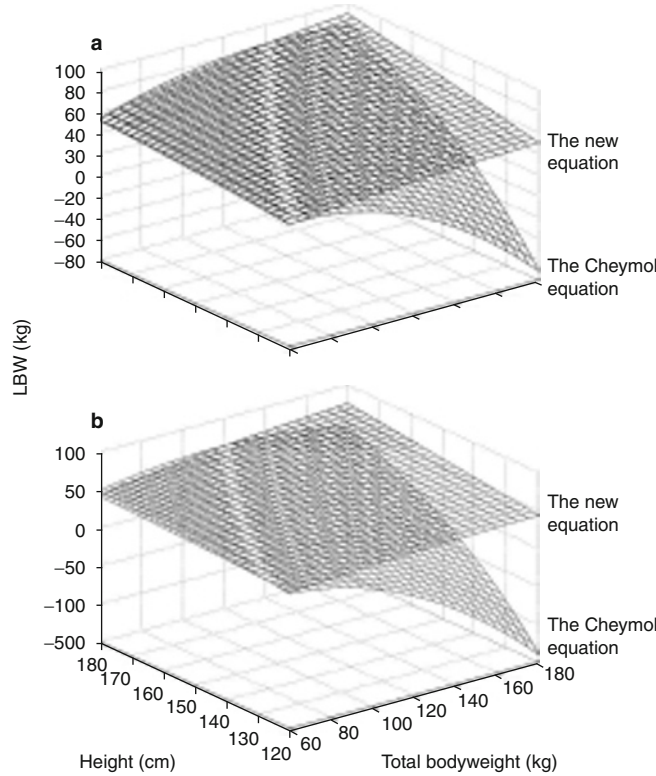

Fig. 6. Estimated lean bodyweight (LBW) for (**a**) males and (**b**) females according to the Cheymol[3] equation and our equations for LBW.

illustrate that the structural form of the relationship between patient demographics and impedance was developed based on *a priori* knowledge rather than on BIA measurements. We therefore believe that the model incorporates biologically reasonable features and hence would be of more use for extrapolation that is inevitable in any clinical application of the equation than a model that was developed from an empirical relationship derived from the data without reference to understanding how impedance of a current through biological tissues might arise. Incorporation of the 'semi-mechanistic' model for impedance into an overall model to predict FFM was based on a standard relationship (Ht^2/Z) that has been described before.[22] This relationship has been found to provide a good predictor of FFM from impedance over a wide range of subject characteristics (aged 18–50 years and FFM 34–96kg).[36] Again we did not change the structural relationship of this model, but rather estimated the parameter values. It was encouraging to note that when we estimated the exponents of the relationship the original form was preferred, i.e. that the exponent for height was two and for predicted impedance was one.

The final model for predicting FFM from patient characteristics is based on bodyweight, height and sex. Given the wide range of bodyweights of subjects enrolled in this study it is likely that the model will have good predictive performance with minimal need for extrapolation to patients who have more extreme BMI values. The predictive performance of the model was assessed using both internal and external evaluation. The external evaluation assessed the ability of the model to predict FFM in patients who were not used for model building. This is a strong test of the ability of the model to perform well when used to predict into a new population. The prediction error was acceptably small, as indicated by the ME of −0.04 and RMSE of 4.39.

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It is also encouraging to note that our model for FFM provides predictions that are very similar to that of the Cheymol/James for subjects with BMI values that are <35 kg/m^2. Hence, for patients of normal weight to moderately obese (which corresponds to the demographics of the subjects in the original James[24] study) either of the predictive equations for LBW/FFM could be used with reasonable accuracy. However, for patients who are morbidly obese it would seem prudent not to use the Cheymol/James equation, and it is in this circumstance that the current work will provide some advantages.

Despite the fact that the model for FFM was developed from the data that had a wide range of bodyweights and BMI (population A), the data used to evaluate the model (population B) were limited to be between the bodyweights of 47.6–131.7kg (BMI values of 18.7–38.4 kg/m^2). Therefore, further work on evaluation would be prudent. A further potential limitation to the study was the use of different BIA instruments at different study sites, which may result in systematic differences in the impedance measurement. However, both instruments were calibrated against a specified reference resistor and were found to produce essentially equivalent results. Based on this empirical test it seems that any difference would indeed be small and of doubtful clinical significance. Additionally, BIA and DXA were performed by different investigators in the different populations. Nevertheless, it has been reported that variation between observer of DXA and BIA measurements is not significant.[37,38]

Conclusion

In summary, we believe that the current work that provides a predictive equation for LBW will be of significant value for clinical use. The scaling of doses of drugs to LBW (when accurately defined) remains a controversial topic and future studies that attempt to find appropriate size descriptors for the obese population, such as PNWT,[9] which are based on LBW, require further consideration.

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References

1. Kopelman PG. Obesity as a medical problem. Nature 2000; 404 (6778): 635-43
2. Green B, Duffull SB. What is the best size descriptor to use for pharmacokinetic studies in the obese? Br J Clin Pharmacol 2004; 58 (2): 119-33
3. Cheymol G. Effects of obesity on pharmacokinetics implications for drug therapy. Clin Pharmacokinet 2000; 39 (3): 215-31
4. Green B, Duffull SB. Development of a dosing strategy for enoxaparin in obese patients. Br J Clin Pharmacol 2002; 56: 96-103
5. Sarubbi Jr FA, Hull JH. Amikacin serum concentrations: prediction of levels and dosage guidelines. Ann Intern Med 1978; 89 (5 Pt 1): 612-8
6. Wulfsohn NL. Succinylcholine dosage based on lean body mass. Can Anaesth Soc J 1972; 19 (4): 360-72
7. Green B, Duffull SB. Caution when lean body weight is used as a size descriptor for obese subjects. Clin Pharmacol Ther 2002; 72 (6): 743-4
8. Morgan DJ, Bray KM. Lean body mass as a predictor of drug dosage: implications for drug therapy. Clin Pharmacokinet 1994; 26 (4): 292-307
9. Duffull SB, Dooley MJ, Green B, et al. A standard weight descriptor for dose adjustment in the obese patient: what is the best size descriptor to use for pharmacokinetic studies in the obese? Clin Pharmacokinet 2004; 43 (15): 1167-78
10. Roche AF, Heymsfield SB, Lohman TG, editors. Human body composition. Champaign (IL): Human Kinetics, 1996
11. Pi-Sunyer FX. Obesity: criteria and classification. Proc Nutr Soc 2000; 59 (4): 505-9
12. Bioelectrical impedance analysis in body composition measurement. Bethesda (MD): National Institutes of Health, Public Health Service, 1994 Dec 12-14
13. Liedtke RJ. Fundamentals of bioelectrical impedance analysis [online]. Available from URL: http://www.rjlsystems.com/docs/bia_info/fundamentals [Accessed 2005 Jul 3]
14. Ellis KJ. Human body composition: in vivo methods. Physiol Rev 2000; 80 (2): 649-80
15. Stewart AD, Hannan WJ. Prediction of fat and fat-free mass in male athletes using dual x-ray absorptiometry as the reference method. J Sports Sci 2000; 18 (4): 263-74
16. Pietrobelli A, Formica C, Wang Z, et al. Dual-energy x-ray absorptiometry body composition model: review of physical concepts. Am J Physiol 1996; 271 (6 Pt 1): E941-51
17. Blake G, Fogelman I. Technical principles of dual energy x-ray absorptiometry. Semin Nucl Med 1997; 37: 210-28
18. Heymsfield SB, Smith R, Aulet M, et al. Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. Am J Clin Nutr 1990; 52 (2): 214-8
19. Beal SL, Sheiner LB. NONMEM user's guide (Pt I). San Francisco (CA): University of California, 1992

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20. Sheiner LB, Beal SL. Some suggestions for measuring predictive performance. J Pharmacokinet Biopharm 1981; 9 (4): 503-12
21. Akaike H. A new look at the statistical model identification. IEEE Trans Automat Contr 1974; 19: 716-23
22. Lukaski HC, Johnson PE, Bolonchuk WW, et al. Assessment of fat-free mass using bioelectrical impedance measurements of the human body. Am J Clin Nutr 1985; 41 (4): 810-7
23. Lohman TG. Advances in body composition assessment. Champaign (IL): Human Kinetics, 1992
24. James W. Research on obesity. London: Her Majesty's Stationery Office, 1976
25. Womersley J, Boddy K, King PC, et al. A comparison of the fat-free mass of young adults estimated by anthropometry, body density and total body potassium content. Clin Sci 1972; 43 (3): 469-75
26. Hume R, Weyers E. Relationship between total body water and surface area in normal and obese subjects. J Clin Pathol 1971; 24 (3): 234-8
27. Boddy K, King PC, Hume R, et al. The relation of total body potassium to height, weight, and age in normal adults. J Clin Pathol 1972; 25 (6): 512-7
28. Anon. Obesity: preventing and managing the global epidemic. Report of a WHO consultation on obesity. Geneva: World Health Organization, 1997 Jun 3-5
29. Black D, James WPT, Besser GM, et al. Obesity: a report of the Royal College of Physicians. J R Coll Physicians Lond 1983; 17 (1): 5-65
30. Garrow JS, Webster J. Quetelet's index (W/H2) as a measure of fatness. Int J Obes 1985; 9 (2): 147-53
31. Slaughter MH, Lohman TG, Boileau RA, et al. Skinfold equations for estimation of body fatness in children and youth. Hum Biol 1988; 60 (5): 709-23
32. Malina RM, Katzmarzyk PT. Validity of the body mass index as an indicator of the risk and presence of overweight in adolescents. Am J Clin Nutr 1999; 70 (1): 131-6S
33. Sarria A, Garcia-Llop LA, Moreno LA, et al. Skinfold thickness measurements are better predictors of body fat percentage than body mass index in male Spanish children and adolescents. Eur J Clin Nutr 1998; 52 (8): 573-6
34. Gray DS, Bray GA, Bauer M, et al. Skinfold thickness measurements in obese subjects. Am J Clin Nutr 1990; 51 (4): 571-7
35. Kyle UG, Genton L, Karsegard L, et al. Single prediction equation for bioelectrical impedance analysis in adults aged 20-94 years. Nutrition 2001; 17 (3): 248-53
36. Lukaski HC, Bolonchuk WW, Hall CB, et al. Validation of tetrapolar bioelectrical impedance method to assess human body composition. J Appl Physiol 1986; 60 (4): 1327-32
37. Thomsen TK, Jensen VJ, Henriksen MG. In vivo measurement of human body composition by dual-energy x-ray absorptiometry (DXA). Eur J Surg 1998; 164 (2): 133-7
38. Vettorazzi C, Smits E, Solomons NW. The interobserver reproducibility of bioelectrical impedance analysis measurements in infants and toddlers. J Pediatr Gastroenterol Nutr 1994; 19 (3): 277-82

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