Lean body mass-based standardized uptake value, derived from a predictive equation, might be misleading in PET studies

Taner Erselcan, Bulent Turgut, Derya Dogan, Semra Ozdemir

Department of Nuclear Medicine, Cumhuriyet University School of Medicine, P.K. 806 Sivas, Turkey

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Abstract. The standardized uptake value (SUV) has gained recognition in recent years as a semiquantitative evaluation parameter in positron emission tomography (PET) studies. However, there is as yet no consensus on the way in which this index should be determined. One of the confusing factors is the normalisation procedure. Among the proposed anthropometric parameters for normalisation is lean body mass (LBM); LBM has been determined by using a predictive equation in most if not all of the studies. In the present study, we assessed the degree of agreement of various LBM predictive equations with a reference method. Secondly, we evaluated the impact of predicted LBM values on a hypothetical value of 2.5 SUV, normalised to LBM (SUV_{LBM}), by using various equations. The study population consisted of 153 women, aged 32.3±11.8 years (mean±SD), with a height of 1.61±0.06 m, a weight of 71.1±17.5 kg, a body surface area of 1.77±0.22 m^2 and a body mass index of 27.6±6.9 kg/m^2. LBM (44.2±6.6 kg) was measured by a dual-energy X-ray absorptiometry (DEXA) method. A total of nine equations from the literature were evaluated, four of them from recent PET studies. Although there was significant correlation between predicted and measured LBM values, 95% limits of agreement determined by the Bland and Altman method showed a wide range of variation in predicted LBM values as compared with DEXA, no matter which predictive equation was used. Moreover, only one predictive equation was not statistically different in the comparison of means (DEXA and predicted LBM values). It was also shown that the predictive equations used in this study yield a wide range of SUV_{LBM} values from 1.78 to 5.16 (29% less or 107% more) for an SUV of 2.5. In conclusion, this study suggests that estimation of LBM by use of a predictive equation may cause substantial error for an individual, and that if LBM is chosen for the SUV normalisation procedure, it should be measured, not predicted.

Keywords: Lean body mass – DEXA – Standardized uptake value – SUV – PET

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Taner Erselcan (✉)
Department of Nuclear Medicine,
Cumhuriyet University School of Medicine,
P.K. 806 Sivas, Turkey
e-mail: erselcan@cumhuriyet.edu.tr
Tel.: +90-346-2191300 ext. 2701, Fax: +90-346-2191284

Introduction

The standardized uptake value (SUV), which is defined as the ratio of activity in tissue per millilitre to the activity in the injected dose per kilogram patient body weight (BW), has gained recognition in recent years as a semiquantitative evaluation parameter in positron emission tomography (PET) studies. The initial rationale for its use was the observed increase in the uptake value of 2-[fluorine-18]fluorodeoxy-D-glucose (FDG) with increasing body weight [1]. SUV has been proposed as a simple index of tissue and tumour accumulation of FDG that is independent of patient size [2]. Some authors have even reported SUV thresholds as an indicator of malignancy or prognosis [3, 4]. On the other hand, leaving aside the discussions as to its validity, there is no consensus on the way in which this index should be determined [5, 6]. It seems that the selected mode of normalisation, using BW, body surface area (BSA) or lean body mass (LBM), is one source of the variation in SUV results, as are lesion size and the method of count determination (at the lesion level or blood glucose level) in FDG studies. Within the framework of attempting to identify the most appropriate physiological parameter for application in the SUV normalisation process, some have proposed use of the LBM [7] or BSA [8]; others suggest use of the blood glucose level [9], while BW is generally taken into consideration. Yeung et al. even recently reported that more constant values were obtained for SUV normalised to LBM (SUV_{LBM}) after the "normalisation of a normalised" parameter, with the SUV first being normalised to LBM, and then to BSA [10].

It is interesting that in such studies, predictive equations, or in other words the regression formulae, are widely preferred in the determination of the LBM. Before further discussion on the most appropriate physiological parameter in SUV calculations, the accuracy of using regression equation-based LBM estimations should be determined with the aim of eliminating other sources of variation (or bias).

LBM can be accurately measured by the dual-energy X-ray absorptiometry (DEXA) method. Although DEXA is not yet considered to be "the gold standard" for measuring body composition, it is one of the best reference methods [11, 12, 13]. DEXA measures the soft tissue and bone mass independently and then separates the soft tissue into lean and fat mass. DEXA estimates the LBM without making assumptions regarding fat mass, total body potassium, total body water or body density, which are the basis of most of the hand-held body composition analysis techniques (e.g. anthropometric, bioelectrical impedance) or the LBM predictive equations [14, 15]. Accurate detection of small differences in hydration [16, 17], changes in soft tissue mass [18] or changes in treatment-related fat mass have been reported by DEXA measurements [19].

This study was undertaken to test the hypothesis that predictive equation-based LBM calculation is an important source of variation in LBM-based SUV results. To test this hypothesis, in a first step, the predicted LBM values obtained with various predictive equations were compared with the results of DEXA measurement in a patient population with no serious health problems. In a second step, the effect of formula-based LBM determination on a hypothetical SUV of 2.5 was examined.

Materials and methods

Patient population. This study is a retrospective analysis of 153 consecutive female patients. Some had taken part in a previous study of bone mass modification in polycystic ovary disease (44%, *n*=68), while the others had been referred either for obesity monitoring (25%, *n*=38) or for whole-body total mineral determination (31%, *n*=47) by the dual-energy X-ray absorptiometry method, between 1997 and 2001 [20]. The only pre-set exclusion criterion was an age younger than 20 years or older than 70 years, as in most of the studies dealing with anthropometric predictive equations. The ethical committee approved the study and the study subjects gave their informed consent.

Body composition analysis. In all of the subjects, body weight and height were measured by well-calibrated hospital scales before the examination. After overnight fasting, subjects underwent a whole-body DEXA scan performed in standard array mode with a speed of 25 cm/min (Hologic 4500 W, Acclaim, USA). The analysis procedure for the raw scan data was quite simple, as it required only the delineation of the body parts by the operator. The rest of the analysis was done automatically by the system software and the measurement results for a subject were reported in total or according to body region as fat mass, LBM and bone mineral content in grams. The long-term in vitro precision error (as measured by the coefficient of variation) in bone mineral density measurement was 0.39% between 1997 and 2001. The relatively short-term precision error in fat mass measurement was 2%–3%, as detailed elsewhere [21]. The sum of measured LBM and total bone mineral content (which is the same as the "fat-free mass") of patients was taken into consideration as the variable of interest, LBM_{DEXA} (LBM measured by DEXA), to obtain comparable values with the predictive equations, although the term LBM does not include the bone mineral content. As the terms LBM and fat-free mass are used interchangeably, but incorrectly, in reality all of the formulae evaluated here in fact predict the fat-free mass, not the LBM [22].

Formulae used in LBM calculations. A total of nine predictive equations were evaluated. Four of them (F1–F4) have been used in recent PET studies within the context of SUV_{LBM} calculations. The others (F5–F9) have been reported by various authors but, to our knowledge have not been applied in a PET study. These predictive equations were as follows:

$$\mathrm{LBM(kg)} = \mathrm{weight} - \{\mathrm{weight} \times [(1.20 \times \mathrm{weight}/\mathrm{height}^2) + (0.23 \times \mathrm{age}) - 5.4]/100\} \quad \text{(F1)}$$

$$\mathrm{LBM(kg)} = 1.07 \times \mathrm{weight} - 148 \times (\mathrm{weight}/\mathrm{height}^2) \quad \text{(F2)}$$

$$\mathrm{LBM(kg)} = 45.5 + 0.91 \times (\mathrm{height} - 152) \quad \text{(F3)}$$

$$\mathrm{LBM(kg)} = 45.5 + (0.91 \times \mathrm{height} - 152) \quad \text{(F4)}$$

$$\mathrm{LBM(kg)} = \mathrm{weight} - \{\mathrm{weight} \times [71.3 - (974 \times \mathrm{height}^2/\mathrm{weight})/100]\} \quad \text{(F5)}$$

$$\mathrm{LBM(kg)} = 0.150 \times \mathrm{weight} + 0.224 \times \mathrm{height} - 0.092 \times \mathrm{age} + 1.31 \quad \text{(F6)}$$

$$\mathrm{LBM\ (kg)} = \mathrm{weight} - \left\{\mathrm{weight} \times \left[64.5 - 848 \times (\mathrm{height}^2/\mathrm{weight}) + (0.079 \times \mathrm{age}) - (16.4 \times \mathrm{sex}) + (0.05 \times \mathrm{sex} \times \mathrm{age}) + 39 \times \mathrm{sex} \times (\mathrm{height}^2/\mathrm{weight})\right]/100\right\} \quad \text{(F7)}$$

$$\mathrm{LBM(kg)} = \mathrm{weight} - \{\mathrm{weight} \times [76.0 - 1097.8 \times (\mathrm{height}^2/\mathrm{weight}) + 0.053 \times \mathrm{age}]/100\} \quad \text{(F8)}$$

$$\mathrm{LBM(kg)} = \mathrm{weight} - [(0.61 \times \mathrm{weight}) - (0.23 \times \mathrm{height}) + (0.04 \times \mathrm{age}) + 15] \quad \text{(F9)}$$

The exact forms of the formulae F1 [8], F2 [7], F3 [1] and F4 [23] were used as they were expressed in the original reports. Equations F5 [24] and F9 [27] are re-arranged forms of the originally reported formulae for estimation of percentage body fat. Equation F6 [25] was originally reported for estimation of fat free mass. Equation F7 [26] is the re-arranged form of the originally reported formula for estimation of percentage body fat, based on a four-compartment model, from a recent multicentre study with a multiracial patient population (white and African Americans) [26]. Equation F8 [26] is the re-arranged form of the originally reported formula for estimation of percentage body fat, derived from DEXA measurements in the white female population. The weight is expressed in kg in all of the formulae. The height is in m in F1, F5, F7 and F8, and in cm in F2, F3, F4, F6 and F9. Age is in years, and in F7 sex =0 for female and 1 for male.

BSA (m^2) was calculated by the formula $(\mathrm{weight} \times \mathrm{height}/3600)^{1/2}$ [8]. Body mass index (BMI) was calculated as: $\mathrm{weight}/\mathrm{height}^2$

(kg/m^2). A woman with a BMI>27.3 was accepted as overweight according to the definition of National Center for Health Statistics, USA [28].

In order to assess the impact of variation in LBM on an SUV, a hypothetical SUV_{LBM} of 2.5 and an average LBM value of 45 kg, as if measured by DEXA, were chosen. Then, 95% upper and lower agreement limits of a predicted LBM value for 45 kg with each formula cited above were calculated according to the method of Bland and Altman [29]. In the next step, SUV_{LBM} was recalculated along with these limits using the equation $SUV_{LBM}=C/LBM(g)$, where C represents "tissue activity concentration/injected dose" and is assumed to be a constant, while the variable LBM takes values according to 95% agreement limits. This equation is the rearranged form of the formula

$$SUV_{LBM} = \text{tissueconcentration(MBq/g)} / \text{injecteddose(MBq)/LBM(g)}$$

from [8].

Statistics. LBM_{DEXA} values in each study subject were compared with each of the LBM values obtained using the predictive equations ($LBM_{F1–F9}$). The data are expressed as mean ± standard deviation (mean±SD). The Kolmogorov-Smirnov statistic, with a Lilliefors significance level, was used to test the distribution normality. The data were analysed using three different statistical approaches. First, linear regression analysis was used to test the relationship between LBM_{DEXA} and $LBM_{F1–F9}$. Second, paired t test was used to examine the difference between LBM_{DEXA} and $LBM_{F1–F9}$. Third, the bias and 95% limits of agreement between LBM_{DEXA} and $LBM_{F1–F9}$ were calculated according to the method described by Bland and Altman, to assess the agreement between LBM_{DEXA} and $LBM_{F1–F9}$ [29]. Briefly, this was done by plotting the difference between the criterion (DEXA) and predictor (F1–F9) LBM values for each subject against their mean value, the mean being the best available estimate of the true value. The statistical software SPSS was used in statistical analysis. Statistical significance was set at $P<0.05$ for all tests.

Table 1. Characteristics of the study subjects (n=153)

	Mean	Std. deviation	Range
Age (yrs)	32.3	11.8	20–68
Height (m)	1.61	0.06	1.44–1.80
Weight (kg)	71.1	17.5	43–117
BMI (kg/m^2)	27.6	6.9	17.0–45.5
BSA (m^2)	1.77	0.22	1.38–2.32
LBM_{DEXA} (kg)	44.2	6.6	29.5–65.3

BMI, Body mass index; BSA, body surface area; LBM_{DEXA}, lean body mass measured by the dual-energy X-ray absorptiometry method

Results

The patient population comprised relatively young women, of whom 57% (n=87) were of normal weight (BMI <27.3) and 43% (n=66) were overweight (BMI >27.3) (Table 1).

Relationship between predicted ($LBM_{F1–F9}$) and measured (LBM_{DEXA}) LBM values

The regression models (slope, intercept) and the standard error of estimation (SEE) values in linear regression analysis between LBM_{DEXA} and $LBM_{F1–F9}$ are given in Table 2. The equations for the lines describing the relationship between LBM_{DEXA} and F3 and between LBM_{DEXA} and F4 were markedly different from the equation for the line of identity. The best slope and intercept values were obtained by F9, while the least SEE was achieved with F6. The regression coefficients (R^2) varied from 0.11 (F3, F4) to 0.74 (F7). Thus, even F7 explained only 74% of the variance of LBM_{DEXA}. Unexplained variance of LBM_{DEXA} was quite high, reaching 89% in the case of F3 and F4.

Table 2. Comparison of measured (by DEXA) and estimated (by predictive equations, F1–F9) LBM values (n=153)

Predictive equations	LBM (kg) (mean±SD)	Linear regression[a]					Bias and 95% limits of agreement (kg)	P values for difference[b]
		Slope	Intercept	SEE	R^2*	Adj. R^2 (n=87)**		
F1	44.5±5.0	0.61	17.5	3.0	0.64	0.51	–0.4±7.9	0.04
F2	45.4±4.4	0.50	23.1	2.9	0.56	0.47	–1.2±8.7	<0.001
F3	53.5±5.3	0.27	41.7	5.0	0.11	0.26	–9.4±13.9	<0.0001
F4	39.9±5.3	0.27	28.0	5.0	0.11	0.26	4.3±13.9	<0.0001
F5	45.6±5.4	0.69	15.0	2.9	0.71	0.47	–1.4±7.1	<0.0001
F6	45.0±2.9	0.37	28.7	1.7	0.68	0.46	–0.8±8.9	0.02
F7	45.3±5.8	0.76	11.7	3.0	0.74	0.50	–1.1±6.8	<0.001
F8	44.3±4.4	0.56	19.3	2.4	0.72	0.47	–0.1±7.4	0.60
F9	48.4±6.9	0.88	9.5	3.7	0.71	0.48	–4.2±7.5	<0.001

SEE, standard error of estimation; Bias, mean difference between measured (DEXA) and predicted (F1–F9) LBM values; 95% limits of agreement, ±2SD of mean differences

*$P<0.001$ for all

**Adjusted R^2, in normal weight subjects

[a] Slope, intercept, SEE and R^2 values are for the whole group of patients (n=153)

[b] Based on paired t test

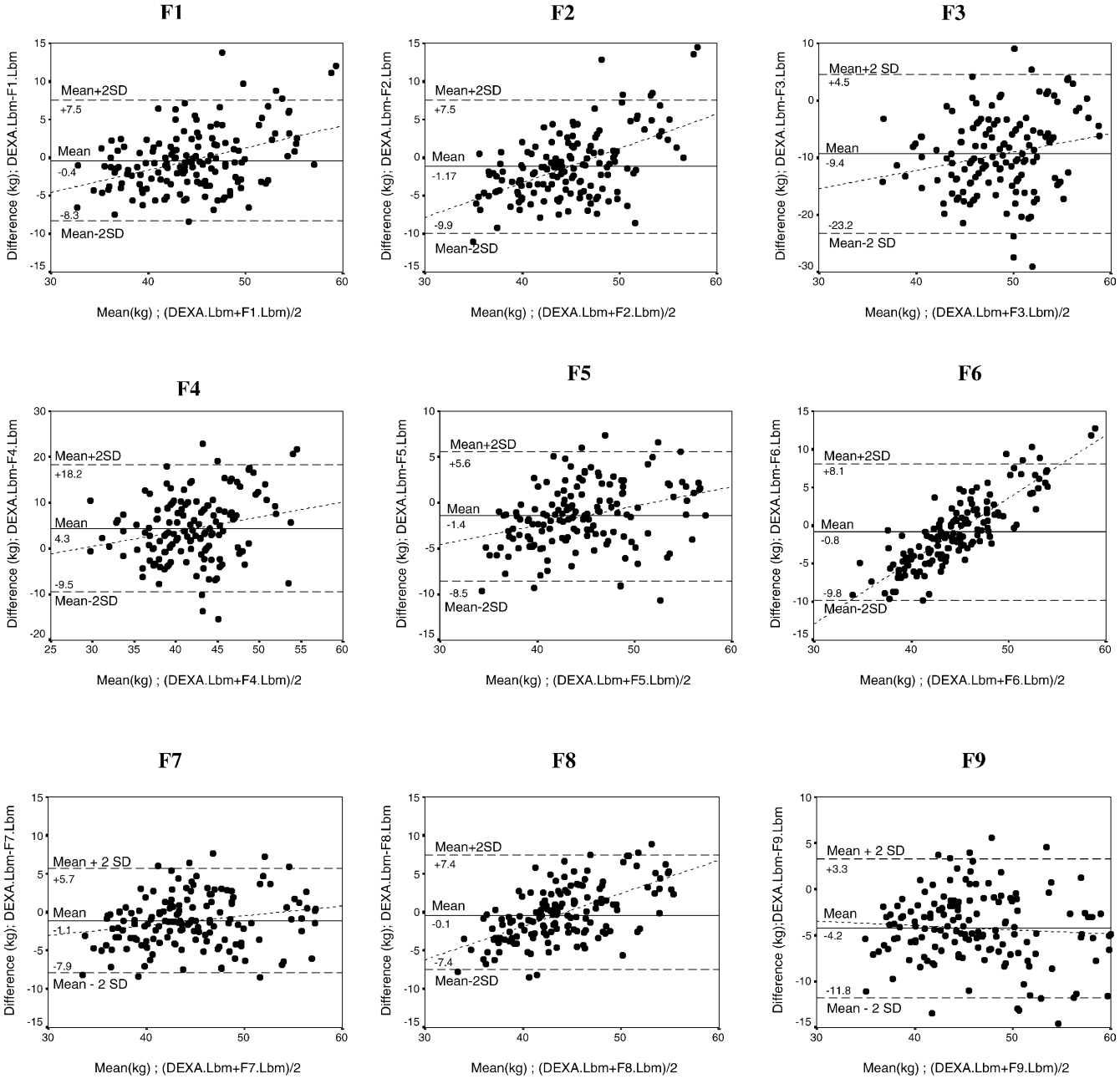

Fig. 1. Comparisons of predicted (F1–F9) and measured (DEXA) LBM values using Bland and Altman plots. The *solid line* represents the mean difference, and the *dotted lines* represent the upper and lower limits of agreement (mean±2SD)

The analysis was repeated with each of the formulae in the subgroups of normal weight and overweight patients (based on the BMI index) to test the hypothesis that this quite high unexplained variance might have been due to overweight patients in the study group. The contribution of weight to the variation could be partly explained only in two equations, as 15% variance in F3 and F4. However, the unexplained variance increased markedly for the rest of the formulae when the analysis was limited to normal weight patients (Table 2).

The predictive equation derived from the present study population by using weight, height and age as independent variables in a multiple stepwise regression analysis was:

$$\mathrm{LBM(kg)} = 0.326 \times \mathrm{weight(kg)} + 0.257 \times \mathrm{height(cm} - 0.119 \times \mathrm{age(yr)} - 16.48$$

(SEE=3.4, r=0.86, P<0.001).

Comparison of predicted ($LBM_{F1–F9}$) and measured (LBM_{DEXA}) LBM values

The LBM values predicted by eight of the equations (F1–F7 and F9) were significantly different from the

Table 3. Variation in LBM and SUV for an individual with LBM_{DEXA}=45 kg and SUV=2.5

Equation	95% lower limit of agreement			95% upper limit of agreement		
	LBM (kg)	SUV_{LBM}	Difference (%)	LBM (kg)	SUV_{LBM}	Difference (%)
F1	36.7	3.06	+23	52.6	2.14	–14
F2	35.1	3.20	+28	52.5	2.14	–14
F3	21.8	5.16	+107	49.5	2.27	–9
F4	35.5	3.17	+27	63.2	1.78	–29
F5	36.5	3.08	+23	50.6	2.22	–11
F6	35.2	3.19	+28	53.1	2.12	–15
F7	37.1	3.03	+21	50.7	2.22	–11
F8	37.6	3.00	+20	52.4	2.15	–14
F9	33.8	3.32	+26	47.7	2.36	–6

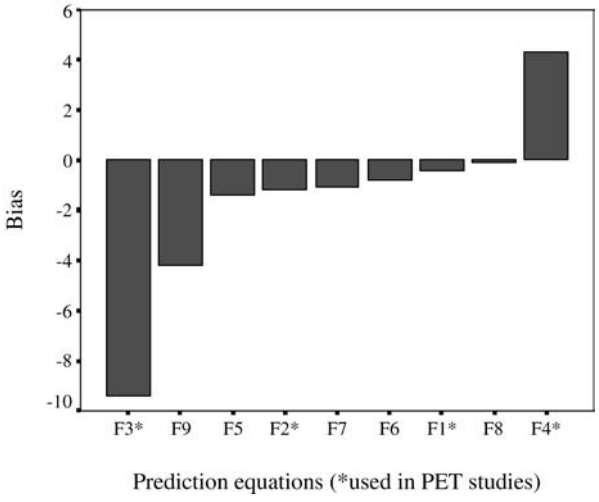

Fig. 2. Distribution of bias values for the predictive equations in LBM estimation, as compared with DEXA

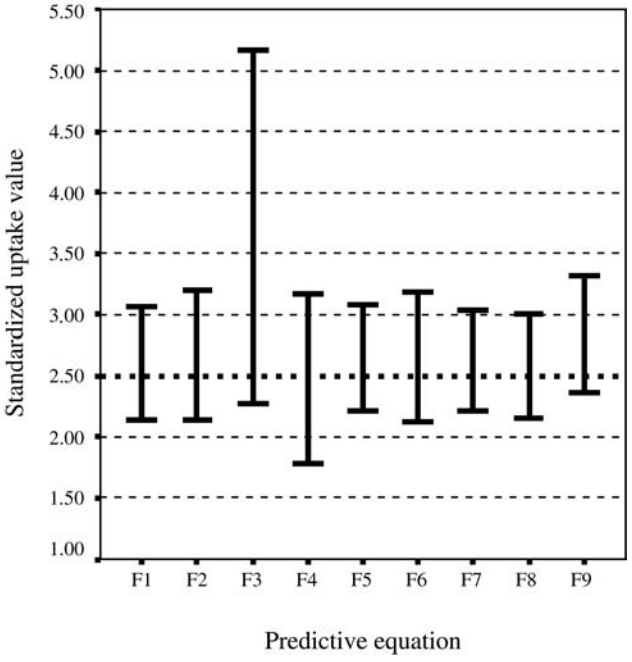

Fig. 3. Variation in predefined SUV of 2.5 according to various predictive equations based on LBM values. The 95% upper and lower limits of agreement are indicated

measured ones, according to the paired *t* test (Table 2). The difference was not statistically significant only between LBM_{DEXA} and F8 (*P*=0.60).

Agreement of the predictive equations with DEXA in LBM estimation

The individual bias values and the 95% limits of agreement between LBM_{DEXA} and $LBM_{F1–F9}$ are given in Table 2. The Bland and Altman plots of LBM_{DEXA} against each of the LBMs obtained with the nine predictive equations are shown in Fig. 1.

Although the relations between predicted and measured LBM values were statistically significant in regression analysis, re-analysis of the data using the Bland and Altman method showed a wide range of bias between each of the predictive equations and the DEXA method (Fig. 1), from –9.4 to 4.3 kg. In other words, there was lack of agreement between estimated and measured LBM values, demonstrated by large limits of agreement, irrespective of the particular bias. For example, for an individual, the LBM value estimated by F1 ranged from 8.3 kg below to 7.6 kg above that measured via DEXA. The situation was even worse for F3, the estimated LBM value ranging from 23.2 kg below to 4.5 kg above that measured via DEXA; this indicates an obvious lack of agreement between the two methods. The disagreement was a form of proportional error in all of the equations, as the difference was significantly related to the magnitude of estimation. The strongest such relation was observed in the case of F6, the difference between LBM_{DEXA} and F6 becoming more positive with increasing magnitude (Fig. 1, F6). Repeating the same analysis by log transformation of the variables did not change the degree of the relationship between differences and the

magnitude of the estimations (data not shown). Among the predictive equations studied, the least bias was seen with F8 and the greatest with F3 (Table 2, and Fig. 2).

Impact of predicted LBM on an individual SUV of 2.5

Table 3 and Fig. 3 show the 95% upper and lower limits of agreement of the predicted LBM values obtained with each of the formulae (F1–F9) for an individual with an LBM_{DEXA} of 45 kg. According to these new LBM values, a recalculated SUV of 2.5 varied from 5.16 (107% more) to 1.78 (29% less) depending on the predictive equation used (Fig. 3). The most striking range was observed with F3. Using this formula to predict LBM and subsequent SUV normalisation for a value of 2.5 may lead to SUVs from 5.16 to 2.27 for an individual.

Discussion

It is appropriate to discuss the results of this study from several different angles.

Problems in the use of predictive (regression) equations

Each of the formulae used to predict LBM was derived from reference methods employed in body composition studies. For example, the original form of F7 was derived from a four-component model to estimate total body fat that comprises total body water (determined with the aid of tritium or deuterium), body density (determined by underwater weighing) and bone mineral mass (determined by DEXA) [26]. Yet, regression equations always entail some risk of error. The magnitude of error would be acceptable in a population base under some circumstances, but might be misleading for an individual. The statistical term "regression", from a Latin root meaning "going back", was first used by Francis Galton in 1886 [30]. Galton, in an article entitled "Regression towards Mediocrity in Hereditary Stature", related the height of children to the average height of their parents and concluded that the heritability of height was weak. However, the weakness probably lay primarily in his methodology rather than the heritability [30]. Anthropometric predictive equations are strongly population dependent. A large magnitude of error would be expected for an individual if the equations were to be applied to a population that is different in character from the original population from which the equation was derived [31]. On the other hand, it is interesting that in most of the reports, if not in all, predictive equations have been used to estimate LBM for the normalisation of SUV_{LBM} [1, 7, 8, 9, 10, 23, 32]. Some of the authors reported more consistent values when SUV was normalised to LBM [1, 7]. Pieterman et al., however, found the BSA normalisation to be better than the LBM normalisation [8], while Calvo et al. reported no differences when SUVs were normalised to either BSA or LBM [9].

In this study, we investigated the relations, differences and agreement of the various LBM predictive equations using the DEXA method, which is accepted as a reference technique in body composition analysis. Comparison of predictive equations from PET studies with the reference method indicated high errors in the prediction of LBM, with a bias ranging from –9.4 to 4.3 kg for an individual, despite the presence of various but statistically significant associations between LBM_{DEXA} and $LBM_{F1–F9}$. It was also shown that this variation yielded a wide range of SUV_{LBM} values from 1.78 to 5.16 (29% less to 107% more) for an individual with an SUV value of 2.5 (Table 3). It should be stressed that the existence of a good correlation between measured and predicted LBM values neither indicates agreement between the techniques nor justifies their interchangeable use [29].

The diversity of SUV_{LBM} results may depend not only on the errors originating from limitations of the predictive equations, but also on the differences in the sample type or population on which the particular predictive equation was originally based. In most of the PET studies reporting variation in SUV_{LBM}, the study population probably consisted of lean and obese subjects together, with a weight range from 42 to 132 kg [7] or from 35 to 135 kg [23]. Indeed, in one of the most comprehensive studies evaluating predictive equations, Fuller et al. observed wide and unacceptable variability in the estimation of body composition by the predictive equations in obese patients [31]. Another striking example in this context is that, although the patient population comprised mainly adults in the study of Sugawara et al. and children in the study of Yeung et al., both authors used the same predictive equation in SUV_{LBM} calculations [7, 10]. We are not sure whether this formula is universally applicable, but it would not be surprising to see reports with varying or contradictory results if an equation originally derived from lean subjects were to be applied to obese patients or one derived from an adult population were to be applied to a paediatric group. In order to better show the agreement errors, we did not intend to find an equation more applicable to our patient population, or to use weight limits. In fact, in most studies evaluating the SUVs, the study population has consisted of patients with an even wider range of weight than the population in the present study, as mentioned above. Moreover the contribution of weight to the variation could be partly explained only in two equations (F3, F4) when analysis was repeated with normal weight patients. In the rest of the equations, the weight limitation resulted in an increase in variance, which suggests that the original population used to derive these predictive equations consisted of some overweight people and that application of these formulae in patients of normal weight would increase bias.

Another constraint in using predictive equations lies in the differences between ethnic groups. Indeed, Gallagher et al. recently reported that Asians have a different body fat percentage than African Americans and white subjects [26]. Although the patient population in the present study consisted of white females and the equation F8 was derived from DEXA measurements in a white female population, it did not show good agreement, either. However, F8 was shown to yield the least bias and best correlation with DEXA among the equations, with no statistically significant difference as compared with LBM_{DEXA}. If F8 were used to estimate LBM, an individual's LBM would be between 7.4 kg more and 7.4 kg less. In this case an SUV of 2.5 normalised to LBM would be 20% more (3.00) or 14% less (2.15) (Table 3).

Turning to F1, the predictive formula used by Pieterman et al. [8] seems to be a rearranged version of the formula suggested by Deurenberg et al. [33], though its origin was not stated. Fuller et al. reported substantial errors when they compared Deurenberg et al.'s formula with reference methods in obese women: the predicted LBM differed by 7.8±18.1 kg as compared with deuterium dilution, by 9.0±17.3 kg as compared with densitometry and by 8.2±17.4 kg as compared with the three-component model [31].

It is also significant that body composition may show important variations in disease states, potentially rendering invalid the application of predictive equations, including those based on weight, height or age [22, 34]. In a number of chronic diseases, body wasting is characterized by the involuntary loss of body cell mass (BCM), which is metabolically active tissue (BCM = LBM–extracellular water–extracellular solids). A well-known example is HIV AIDS-associated wasting. In this disorder, while body fat is preserved, weight loss occurs due to the depletion of LBM, leading to muscle weakness and organ failure [35]. Since body composition analysis by DEXA is a relatively new technique and body component estimation using solely anthropometric indices is a debatable concept, few studies have compared these two techniques. Among those that have, Herd et al. found very good correlation between DEXA and fat mass estimation by using F9, with r=0.91 (or R^2=0.83) and SEE=2.4 kg, in 111 normal Caucasian women [36]. In the present study, the mean fat mass was measured as 26.3±12.6 kg using the DEXA method and calculated as 22.6±10.9 kg using F9 (R^2=0.85). The results of these two studies seem to be comparable when R^2 values are considered. However, the mean difference between measured and predicted fat mass values averaged 3.6±4.9 kg in our study, whereas it was reported to be less than 1 kg (0.8±0.2) in the study of Herd et al. A simple explanation for this discrepancy would be the differences in the study populations; for example, the patient population was younger and heavier in the present study.

Would LBM be an appropriate normalisation parameter?

The definition of "normal" implies a denominator in living organisms. In nuclear medicine most efforts have long been focussed on measuring the numerator, as how much or how dense is the tracer uptake. Without a denominator, however, the numbers are meaningless, and the denominator needs as much measurement precision as the numerator. Better precision (as measured by the coefficient of variation) of the denominator can be achieved by shrinking the target compartment so that the contaminant effect of the surrounding compartments on the denominator is eliminated [37]. Assume that uptake of a labelled amino acid is progressively normalised by height, weight, BSA, body mass index, fat-free mass, LBM and finally body cell mass. If the objective is to obtain the minimum variation, then in this case, the smallest compartment fully representing the metabolic journey of the molecule would be the body cell mass. The second would be the LBM. On the other hand, the pharmacokinetic variables of drug clearance and volume of distribution are usually corrected for body weight or body surface area, although the main factors that affect the tissue distribution of drugs are body composition, regional blood flow and the affinity of the drug for plasma proteins and/or tissue components [38]. Obese but otherwise healthy people have larger absolute lean body masses as well as fat masses than non-obese individuals of the same age, gender and height [38]. Drugs with a low or moderate affinity for adipose tissue show a moderate increase in the volume of distribution, and this correlates with the increase in LBM. In this respect it seems logical to take into consideration a body compartment that is in relation with a labelled molecule, instead of body weight or body surface area. Body weight is not an accurate parameter for assessment of changes in body composition, either in health or in disease. In fact, weight loss may not always be due to decrease in fat mass, as in the case of sarcopenia in thyrotoxicosis [39]. Conversely, acid or an increase in LBM may be the reason for weight gain [40]. But sometimes it may not be so easy to foresee the underlying modifications in body composition, as in the case of sarcopenic obesity [41]. Another anthropometric parameter, BSA, which is related to height, is also not an accurate index either for lean body mass or for fat mass. For example, in this study LBM differed by 20% among patients with exactly the same BSA (1.71 m^2, n=6), although the regression coefficients (R^2) were statistically significant between LBM_{DEXA} and height, LBM_{DEXA} and BMI, LBM_{DEXA} and BW, and LBM_{DEXA} and BSA, being 0.11, 0.45, 0.62 and 0.67, respectively (n=153, P<0.001 for all). The fact that the coefficient between LBM_{DEXA} and height was the lowest may explain why the predictive equations F3 and F4 showed higher bias than the others: these formulae were solely based on height.

Review articles on techniques of body composition analysis have been published in this journal and, recently, *Physiol Rev* [15, 22]. Among these techniques, DEXA is safe, requires little cooperation with the subject and does not have to be calibrated against a reference method. One of the acknowledged weaknesses in the assessment of body composition by DEXA is the assumption of a fixed water fraction in LBM. Current DEXA software assumes that LBM contains 73.2% water. However, there is no body composition technique available for routine clinical use that is "assumption-" and "error-free" [15]. The hand-held techniques may show significant disagreement with the reference method, depending on the patient population under consideration [21]. The DEXA method can be used to obtain LBM values instead of regression formulae in the normalisation procedure for PET studies. The whole-body scan takes only 5–6 min. The radiation-absorbed dose in a whole-body DEXA scan, with the device used in the present study, is only 15 μSv [21]. However, in the event of non-availability or when the patient is concerned about radiation exposure, other techniques, such as bioelectrical impedance, can be used so that at least a patient-specific parameter is taken into consideration.

We have shown in this study that wide variation in LBM estimation as compared to a reference method is an inevitable result, no matter which predictive equation is used. This implies that each patient should be treated on an individual basis with respect to body composition and that, if LBM is chosen for the SUV normalisation procedure, it should be measured rather than predicted using regression equations. There is a clear need for studies comparing different normalisation parameters in SUV determination, using "measured" LBM values.

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