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Predicting abdominal adipose tissue among women with familial partial lipodystrophy

Tisha Joy*, Brooke A. Kennedy, Salam Al-Attar, Brian K. Rutt, Robert A. Hegele

Robarts Research Institute and Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada N6A 5K8

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Abstract

The objective of the study was to determine correlations between magnetic resonance imaging (MRI) measures of truncal adiposity (trunk fat percentage [TrF $\%_{MRI}$], visceral adipose tissue [VAT], and subcutaneous abdominal adipose tissue [SAT]), simple clinical measures (body mass index [BMI], waist circumference [WC], and waist-to-hip ratio [WHR]), and bioelectrical impedance analysis (BIA)–derived measures (total fat percentage [TF %] and TrF $\%_{BIA}$) in female patients with familial partial lipodystrophy (FPLD). Our secondary aim was to generate and cross-validate predictive equations for VAT and SAT using these simple clinical and BIA-derived variables. Measures of truncal adiposity were measured using 1.5-T MRI (VAT, SAT, and TrF $\%_{MRI}$) and Tanita (Tokyo, Japan) 8-electrode body composition analyzer BC-418 (TrF $\%_{BIA}$) in 13 female FPLD patients. Pearson correlation coefficients were determined among the various adiposity parameters (BMI, WC, WHR, SAT, VAT, TrF $\%_{MRI}$, TrF $\%_{BIA}$, and TF %). Equations to estimate VAT and SAT were determined among 6 of the 13 FPLD subjects using multilinear regression analysis, and the best equations were then cross-validated in the remaining 7 subjects. Variables entered into the model included age, BMI, WC, WHR, TrF $\%_{BIA}$, and TF %. The TrF $\%_{MRI}$ showed moderate correlation ($r = 0.647$, $P = .02$) with the TrF $\%_{BIA}$, but the discrepancy between the 2 variables increased with increasing truncal adiposity. The strongest correlate for TrF $\%_{MRI}$ was BMI ($r = 0.886$, $P < .0001$). Visceral adipose tissue was poorly associated with simple clinical measures of BMI, WC, and WHR, but was inversely correlated with TF %, TrF $\%_{BIA}$, and SAT. The TF % was the strongest correlate for both SAT and VAT. Thus, the best regression equation for VAT included age, BMI, WC, and TF % ($R^2 = 1.0$), whereas that for SAT only included TF % ($R^2 = 0.75$). The corresponding standard error of the estimate for the predictive equations was approximately 0.03 % and 18.5 % of the mean value of VAT and SAT, respectively. In the cross-validation study, differences between predicted and observed values of SAT were larger than those of VAT. We conclude that, among female FPLD patients, (1) no simple clinical anthropometric measure correlates well with VAT, whereas BMI correlates well with SAT; (2) BIA measure of TF % most strongly correlated with both VAT and SAT; and (3) based on the cross-validation study, VAT but not SAT could be more reliably estimated using the regression equations derived.

1. Introduction

Familial partial lipodystrophy (FPLD) is a rare autosomal dominant disorder, with an estimated prevalence of 1 in 200 000 [1]. It is characterized by progressive loss of subcutaneous adipose tissue in the extremities, typically commencing in puberty, and increasing dorsal, facial, and visceral adipose tissue (VAT) [2-5]. In addition to these changes in body composition, FPLD is associated with the development of several complications including type 2 diabetes mellitus, dyslipidemia, polycystic ovary syndrome (in women), and premature coronary artery disease [6,7].

The diagnosis of FPLD relies heavily on characteristic physical features and relevant pedigree characterization. Once suspected, individuals may undergo genetic confirmation via sequencing of 2 genes responsible for FPLD: lamin A (*LMNA*) and peroxisome proliferator–activated receptor gamma (*PPARG*) [8-12]. Unfortunately, genetic testing is confirmatory in only approximately 50% of FPLD cases; and thus, diagnosis continues to be predominantly clinically oriented [5]. Once diagnosed, management focuses on the prevention of long-term metabolic sequelae.

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* Corresponding author. Department of Medicine, Schulich School of Medicine and Dentistry, University of Western Ontario, PO Box 5777, London, Ontario, Canada N6A 4V2. Tel.: +1 519 646 6296; fax: +1 519 646 6372.

E-mail addresses: tisjoy@hotmail.com (T. Joy), bkennedy@robarts.ca (B.A. Kennedy), salat056@uottawa.ca (S. Al-Attar), brutt@imaging.robarts.ca (B.K. Rutt), hegele@robarts.ca (R.A. Hegele).

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Central, particularly visceral, adiposity has been linked to the development of metabolic sequelae such as insulin resistance, type 2 diabetes mellitus, and cardiovascular disease [13-15]. Thus, proper assessment of body composition is an important mechanism of predicting future complications and can be done using simple clinical measures (such as waist circumference [WC], waist-to-hip ratio [WHR], and body mass index [BMI]), skin fold thickness, bioelectrical impedance analysis (BIA), dual-energy x-ray absorptiometry (DEXA), or more expensive measures such as computed tomography (CT) or magnetic resonance imaging (MRI). Among non-FPLD individuals, simple clinical measures have correlated well with either visceral or total adiposity as measured using MRI, CT, compartment modeling, or BIA [16-19]. However, none of the simple clinical measures (WC, WHR, or BMI) can help distinguish between VAT and subcutaneous abdominal adipose tissue (SAT). Yet, BMI seems to be a useful predictor of SAT in individuals without FPLD, whereas predictive equations for VAT have not entirely been successful [20-22]. Thus, CT and MRI remain the reference standards for assessing VAT and SAT distribution.

Compared with CT and DEXA, BIA is less expensive and not associated with radiation. Yet, BIA remains highly comparable with DEXA so long as patients are not obese and the equations have been validated within the populations tested [23-25]. Although most BIA instruments provide only an estimate of total fat percentage (TF %), the Tanita (Tokyo, Japan) BC-418 can provide estimates of both total and regional adiposity [25]. The TF % measured by Tanita BC-418 vs DEXA has demonstrated no significant differences except among abdominally obese (WC >88 cm) women, in whom BIA demonstrated consistent underestimation for both TF % and trunk fat % (TrF $\%_{BIA}$) [25,26]. Importantly, individuals with FPLD are not uniformly abdominally obese based on WC criteria but are characterized by increased VAT and decreased SAT compared with controls [5]. Thus, quantifying truncal adiposity among female FPLD patients and the correlation of simple clinical or BIA-derived variables with truncal adiposity seems warranted and forms the primary aim of this study. Our secondary aim was to derive and cross-validate predictive equations for VAT and SAT among female FPLD patients using the above simple clinical and BIA-derived measures.

2. Methods

2.1. Study subjects

Subjects with FPLD being followed in the clinic by a single investigator (RAH) were recruited into this study. Individuals were included if they were female, were older than 18 years, and had genetically confirmed FPLD with known mutations in *LMNA*. A total of 13 female FPLD subjects provided written informed consent. The study was approved by the University of Western Ontario Research Ethics Board (11244).

2.2. Anthropometric assessments

All anthropometric and body composition parameters were assessed in the fasting state. Body mass to the nearest 0.1 kg and standing height to the nearest 0.1 cm were measured using a calibrated balance and stadiometer, respectively. Body mass index was calculated using these height and weight determinations. Waist circumference was measured to the nearest 0.1 cm at the iliac crest after normal expiration. Hip circumference was measured at the level of maximal extension of the buttocks when viewed laterally. Mean WC and hip circumference values were determined from 3 measurements using a nonstretchable measuring tape and were used to calculate WHR.

2.3. Bioelectrical impedance analysis

The Tanita 8-contact body composition analyzer Model BC-418 provided measures of TF % and TrF $\%_{BIA}$. Subjects removed their shoes and socks and wore a gown to allow for accurate body composition analysis. The input information included age, height, and body type (all individuals were classified as standard; none as athletic).

2.4. Magnetic resonance imaging for adipose distribution

Magnetic resonance imaging scans were performed on a 1.5-T General Electric Medical Systems Signa Excite, Waukeshau, WI. Specific MRI images were obtained for abdominal transverse sections at the level of L4 for measurements of SAT and VAT (TrF $\%_{MRI}$ was calculated as the sum of SAT and VAT). Quantification of adipose tissue within these areas was performed as previously described [27], and all values are expressed as percentage adipose tissue.

2.5. Data analysis

Data were analyzed using SAS statistical software (Version 9.1; SAS Institute, Cary, NC). Quantitative clinical traits are expressed as mean ± SD and were compared using Student t test from the general linear models procedure, whereas qualitative traits were compared using χ^2 test. Correlations between various body composition parameters were determined by calculation of the Pearson correlation coefficient. A value of P less than .05 was taken as the nominal level of significance for all comparisons.

Multilinear stepwise regression analysis was used to generate equations to predict VAT and SAT from age and simple clinical and BIA-derived measures (WC, WHR, BMI, TF %, and TrF $\%_{BIA}$) of 6 of the 13 women. The equation with the highest R^2 value was selected for cross-validation in the remaining 7 women. The standard error of the estimate (SEE) was calculated [28]. Prediction equations were considered to cross-validate if the measured vs predicted values in the cross-validation group were not significantly different from the line of identity. Agreement between the predicted and observed values for VAT (or SAT) was assessed by the procedure of Bland and Altman [29], whereby the difference (predicted −

Table 1
Baseline characteristics of FPLD subjects

Variable	Mean ± SD	Range
Age	47 ± 15	23-69
BMI (kg/m^2)	24.9 ± 2.5	20.2-30.7
WC (cm)	89.4 ± 8.3	74.6-105.7
WHR	0.94 ± 0.06	0.87-1.08
TF %	28.2 ± 4.7	23.1-40.9
TrF $\%_{BIA}$	23.7 ± 5.9	16.0-38.2
SAT (%)	14.2 ± 10.5	2.8-46.0
VAT (%)	41.6 ± 6.8	35.6-55.1
TrF $\%_{MRI}$	55.8 ± 7.2	45.8-75.0

observed) between the measurements of VAT (or SAT) for each subject is plotted against the mean measurements of the 2 methods. Thus, the Bland and Altman procedure includes calculation of the bias (the mean of the differences between predicted and observed values) and the error (based on the SD of the differences between predicted and observed values).

3. Results

3.1. Baseline characteristics

Thirteen FPLD women were enrolled and completed this study. All FPLD subjects demonstrated known mutations in *LMNA*, predominantly R482Q (data not shown). Baseline characteristics for clinical, BIA, and MRI adipose measurements for all 13 female FPLD patients are listed in Table 1. Four (31%) had diagnosed type 2 diabetes mellitus. Fifty percent of the women were of normal weight, giving a mean BMI of 24.9 kg/m^2. The mean WC was 89.4 cm, with 50% having a WC less than 88 cm. Importantly, there were no significant differences between the development group (n = 6) and the cross-validation group (n = 7) for any of the variables (Table 2).

3.2. Correlation analyses

Using data from all 13 female FPLD patients, Pearson correlation coefficients (r values) between the various body composition parameters are depicted in Table 3. Of the simple clinical measures, BMI and WC showed strong correlations with TrF $\%_{MRI}$ (r = 0.89, $P < .0001$ and r = 0.80, P = .001, respectively), but not with VAT. Only BMI correlated with SAT (r = 0.67, P = .01). Importantly, in this population, WHR was not correlated with any BIA-derived or MRI-derived measure of adiposity. Meanwhile, the strongest correlate for both VAT and SAT was TF % by BIA (r = −0.62, P = .02 and r = 0.88, $P < .0001$, respectively).

The correlation between TrF $\%_{BIA}$ and TrF $\%_{MRI}$ was moderate (r = 0.65, P = .02). It must be noted that, in this study, TrF $\%_{BIA}$ represents trunk fat as a percentage of total body mass, whereas TrF $\%_{MRI}$ represents trunk fat as a percentage of the total mass of the L4 slice evaluated; and therefore, the 2 values will not be identical. Yet, indications of magnitude bias were found when the association between degree of truncal adiposity as assessed by MRI and the mean difference in TrF % between MRI and BIA was plotted in Fig. 1. The discrepancy between TrF $\%_{MRI}$ and TrF $\%_{BIA}$ increases with greater truncal adiposity, signifying the poor reliability of BIA with increasing truncal adiposity.

3.3. Prediction of VAT and SAT

Given the small number of patients with FPLD in our study, the patients were divided almost equally so that predictive equations could be derived from the data of 6 women and cross-validated in the remaining 7 individuals. The best equations derived are listed in Table 4. For VAT, the predictive equation used 4 variables from the model (age, BMI, WC, and TF %) with an R^2 of 1.0 (P = .003) and SEE of 0.01 % units, a value corresponding to approximately 0.03 % of the mean value of VAT as measured by MRI. The removal of TF % from the model for VAT resulted in a predictive equation of VAT = −6.3777 + 1.2563∗WC, having an R^2 of 0.65. Meanwhile, for SAT, the predictive equation only included TF % with an R^2 of 0.75 (P = .03) and SEE of 2.0 % units, a value corresponding to approximately 18.5 % of the mean value

Table 2
Baseline characteristics of FPLD subjects in development (n = 6) and cross-validation (n = 7) groups

Variable	Development (n = 6)		Cross-validation (n = 7)		P value[a]
	Mean ± SD	Range	Mean ± SD	Range	
Age (y)	49 ± 16	23-69	46 ± 14	23-62	.72
With diabetes (n)	1	–	3	–	.31
BMI (kg/m^2)	24.8 ± 2.4	20.2-26.7	24.9 ± 2.8	21.6-30.7	.94
WC (cm)	87.2 ± 3.3	85.8-93.0	91.4 ± 11.0	74.6-105.7	.36
WHR	0.93 ± 0.04	0.87-1.00	0.95 ± 0.07	0.88-1.08	.44
TF %	28.1 ± 3.0	24.0-31.8	28.2 ± 6.1	23.1-40.9	.96
TrF $\%_{BIA}$	23.4 ± 4.6	19.2-29.2	24.0 ± 7.1	16.0-38.2	.85
SAT (%)	11.0 ± 3.6	5.7-15.6	16.9 ± 13.8	2.8-46	.32
VAT (%)	43.2 ± 5.2	38.1-52.4	40.3 ± 8.1	29.0-55.1	.46
TrF $\%_{MRI}$	54.2 ± 5.1	45.8-60.4	57.2 ± 8.8	47.0-75.0	.46

[a] P value derived using Student t test for quantitative traits and χ^2 test for the qualitative trait of having diabetes.

Table 3
Pearson correlation coefficients (*P* value) between truncal adipose measures by MRI and simple clinical or BIA-derived measures

	WC	WHR	TF %	TrF $\%_{BIA}$	TrF $\%_{MRI}$	VAT	SAT
BMI	0.73 (.005)	0.30 (.33)	0.79 (.002)	0.71 (.006)	0.89 (<.0001)	−0.10 (.74)	0.67 (.01)
WC		0.72 (.006)	0.49 (.09)	0.50 (.08)	0.80 (.001)	0.18 (.56)	0.43 (.14)
WHR			0.13 (.67)	0.23 (.45)	0.37 (.22)	0.38 (.20)	0.006 (.98)
TF %				0.97 (<.0001)	0.71 (.007)	−0.62 (.02)	0.88 (<.0001)
TrF $\%_{BIA}$					0.65 (.02)	−0.57 (.04)	0.81 (.0007)
TrF $\%_{MRI}$						−0.13 (.67)	0.77 (.002)
VAT							−0.73 (.004)

of SAT as measured by MRI. The inclusion of TrF $\%_{BIA}$ or of WHR did not alter these equations.

3.4. Cross-validation

Fig. 2A, B demonstrates the relations between predicted and observed values for SAT and VAT in the cross-validation study of the remaining 7 female FPLD patients. The predictive equations tended to overestimate VAT and underestimate SAT, as evidenced in Fig. 3A, B, which plots the differences between values predicted and observed (ie, residuals) against the values predicted. The range of differences between predicted and observed values were 0.62% to +59.5% for VAT and −54.4% to +158.7% for SAT (data not shown). Using Bland-Altman plots to demonstrate bias (Fig. 4A, B), the predicted equation for VAT overestimated VAT by 7.4% units, whereas that for SAT underestimated SAT by 5.8 % units. Consequently, on average, predicted VAT was approximately 18.2 % higher than observed VAT; and predicted SAT was approximately 34.0% lower than observed SAT. Thus, prediction of VAT was associated with less bias than that of SAT.

4. Discussion

In this study, we sought to examine correlates of truncal adiposity (TrF $\%_{MRI}$, VAT, and SAT) using simple clinical (BMI, WC, and WHR) and BIA-derived measures (TrF $\%_{BIA}$ and TF %) as well as to develop and cross-validate equations for predicting VAT and SAT in female patients with FPLD. We found that there was no simple clinical measure that strongly correlated with VAT, whereas BMI strongly correlated with SAT. Yet, of the simple and BIA-derived measures tested, the strongest correlate for both VAT and SAT was TF %. Moreover, within the population of women studied, the predictive equation for VAT was associated with less bias than that for SAT.

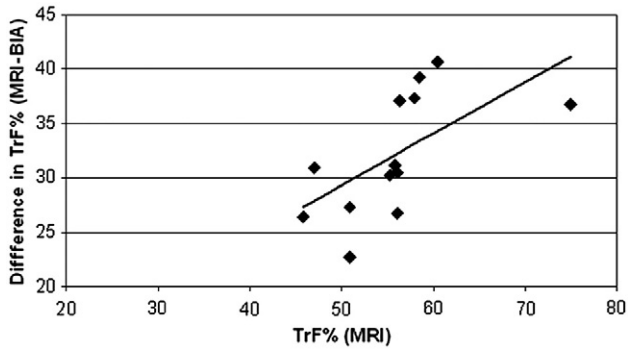

Fig. 1. Discrepancy between TrF $\%_{BIA}$ and TrF $\%_{MRI}$ increases with increasing truncal adiposity. There is a linear increase between the mean differences in TrF % by MRI and BIA (TrF $\%_{MRI}$ − TrF $\%_{BIA}$) and truncal adiposity.

Several studies have demonstrated positive and significant correlations between simple clinical measures or BIA-derived variables and truncal adiposity using DEXA, CT, or MRI [16,17,30-33]. Waist circumference and BMI measurements have been included as part of routine clinical examination given data suggesting their positive associations with VAT and development of metabolic complications [16,32-34]. Waist-to-hip ratio has also been advocated by some as a marker of central obesity and cardiovascular complications [31,35-37]. Meanwhile, BIA has been used for body composition, particularly for addressing dynamic changes in adiposity. The Tanita 8-electrode BIA has been previously shown to agree with DEXA for both TrF % and TF % [25].

Typically, BMI is more strongly correlated with SAT rather than VAT [32,33]; and our findings among women with FPLD support this. However, we found here that TF % was the most strongly correlated variable with VAT, which to our knowledge has not been reported among non-FPLD patients. This is most likely due to the fact that individuals with FPLD have a greater VAT to SAT ratio compared with non-FPLD individuals and also explains our findings of poor correlation between WC or WHR with VAT [5]. Importantly, the lack of correlation between WHR and central adiposity is supported by others [38,39]. We also demonstrated that the reliability of TrF $\%_{BIA}$ (in comparison with TrF $\%_{MRI}$) decreased with increasing truncal adiposity, supporting the results of Neovius et al [26]. Thus, these results demonstrate

Table 4
Prediction equations for VAT and SAT

Equations derived	R^2	SEE
VAT = −7.4426 − 0.1365∗age (y) + 0.3583∗BMI (kg/m^2) + 0.9855∗WC (cm) − 1.3341∗TF % (%)	1.0	0.01
SAT = −18.47 + 1.0495∗TF % (%)	0.75	2.05

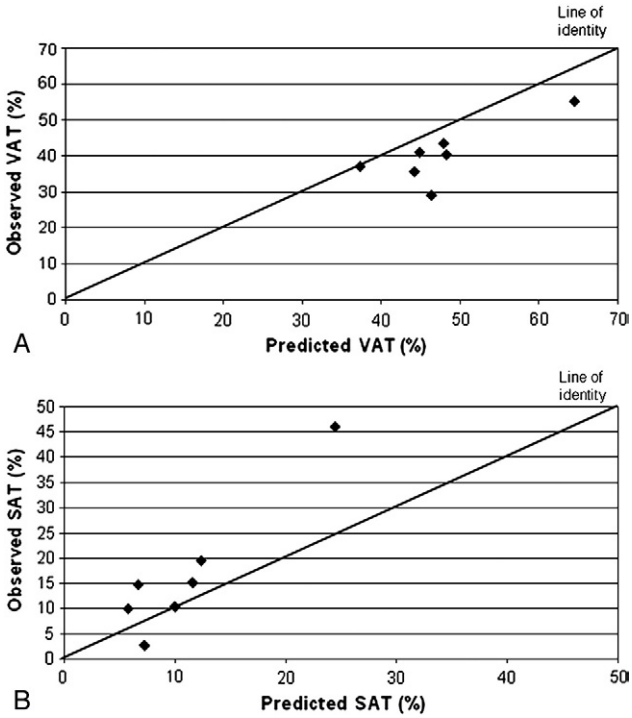

Fig. 2. A, Predicted vs observed values of VAT in cross-validation group. B, Predicted vs observed values of SAT in cross-validation group.

that correlations between simple clinical or BIA-derived variables and measures of truncal adiposity are specific to the populations studied.

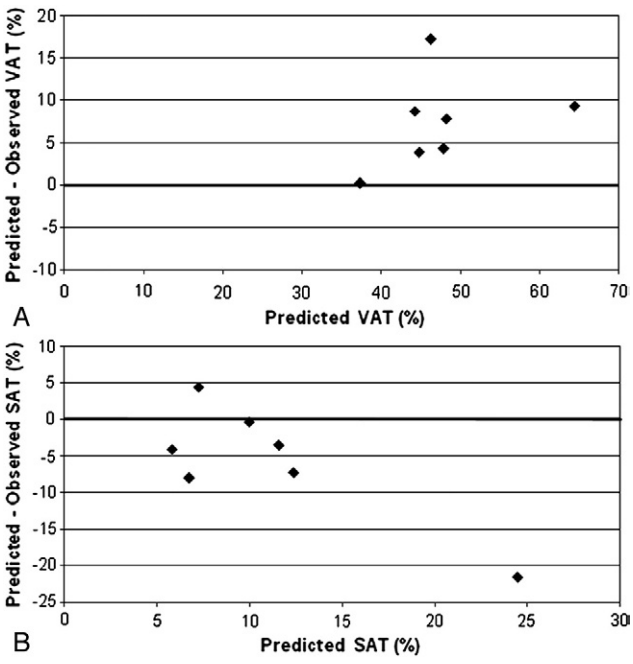

Fig. 3. A, Differences between predicted and observed values of VAT plotted against predicted values of VAT in cross-validation group. B, Differences between predicted and observed values of SAT plotted against predicted values of SAT in cross-validation group.

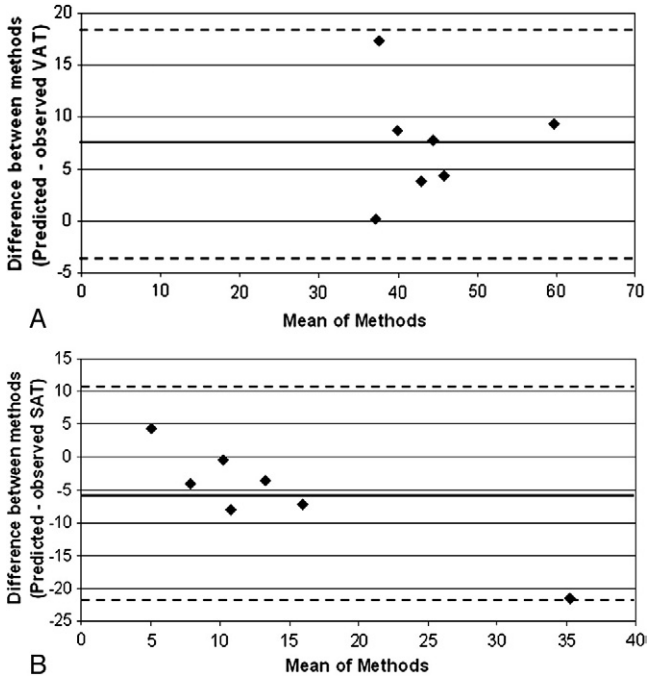

Fig. 4. A, Bland-Altman plot comparing predicted and observed values for VAT. The mean bias was 7.4 (solid line); and the upper and lower limits of agreement (dashed lines) were 18.2 and −3.5, respectively. B, Bland-Altman plot comparing predicted and observed values for SAT. The mean bias was −5.8 (solid line); and the upper and lower limits of agreement (dashed lines) were 10.5 and −22.0, respectively.

Although predictive equations for VAT and SAT have been generated among differing populations [20,22,40-43], none have yet been derived for patients with FPLD. Currently, the diagnosis of FPLD continues to rely heavily on early clinical recognition; and recent methods to quantify and characterize adipose distribution among these individuals have involved the use of highly accurate techniques such as MRI or DEXA [5,44]. However, widespread applicability of these body composition evaluation methods is limited because of cost, availability, or expertise. Thus, deriving simple predictive equations for VAT and SAT may prove to be useful in the future for predicting complications or confirming the diagnosis.

The equations for VAT and SAT derived in this study explained a high degree of variance based on their R^2 values. Importantly, the equation derived for VAT had a higher explained variability (~100%) and a lower SEE (0.03 % of the mean value of VAT measured by MRI) than that derived for SAT. Our equation for predicting VAT among women with FPLD had the highest degree of explained variance compared with other equations generated in non-FPLD populations [20,22,40-43]. Moreover, our equations demonstrated that simple clinical and BIA-derived measures could be useful for predicting VAT in this population, with a low degree of bias in contrast to other equations that relied not only on clinical measures but also on skin fold thickness or CT measures [42,43]. Thus, our equation could be easily applied in clinical practice. Importantly, in cross-validation, the predictive

equations demonstrated a bias of overestimation for VAT and underestimation for SAT. The predictive equation for VAT demonstrated less overall bias compared with the SAT predictive equation (18.2 % overestimation vs 34.0 % underestimation, respectively), again signifying the potential applicability of the VAT predictive equation derived in this study. Conversely, accurate assessment of SAT among women with FPLD remains most reliably done through CT or MRI.

There are a few limitations to this study. First, our results can only be generalized to women affected with FPLD due to *LMNA* mutations. Because FPLD is a rare disorder, we have only been able to report on 13 individuals with *LMNA* mutations. Importantly, the adipose loss is less severe among individuals with *PPARG* mutations rather than *LMNA* mutations [5]. Thus, our results would need to be not only validated in larger studies of female FPLD patients with *LMNA* mutations but also separately derived for those with *PPARG* mutations. Second, we report single measurements for these body composition parameters; and therefore, the agreement of dynamic body composition measurements using these methods in FPLD in response to therapy or weight loss cannot be inferred. Third, we could not assess agreement between TrF $\%_{BIA}$ and TrF $\%_{MRI}$ because these measures were fundamentally different, as explained above. Yet, we were able to demonstrate that BIA became less reliable as a measure of TrF % with increasing adiposity. And finally, the correlation of these parameters with metabolic criteria such as insulin resistance or hypercholesterolemia was not examined. Despite these limitations, we demonstrate that, among women with FPLD due to *LMNA* mutations, BMI remained useful as a correlate for SAT, but no simple clinical measure correlated with VAT. Meanwhile, BIA-derived TF % was the most strongly correlated body composition parameter for both SAT and VAT and, consequently, formed part of the prediction equations for VAT and SAT. The predictive equation of VAT derived in this study was associated with less bias than that of SAT and needs to be validated in a larger study of female FPLD before it can be considered ready for more widespread use.

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