Predictive equation for assessing appendicular lean soft tissue mass using bioelectric impedance analysis in older adults: Effect of body fat distribution

Key Points:

1. The high cost of imaging techniques precludes their use in most clinical settings.
2. Using a portable, safe, quick, and easy to perform BIA device, our findings provide new valid and non-biased model for appendicular lean soft tissue estimate in older adults.
3. The new model will have practical skeletal muscle index monitoring

Figure

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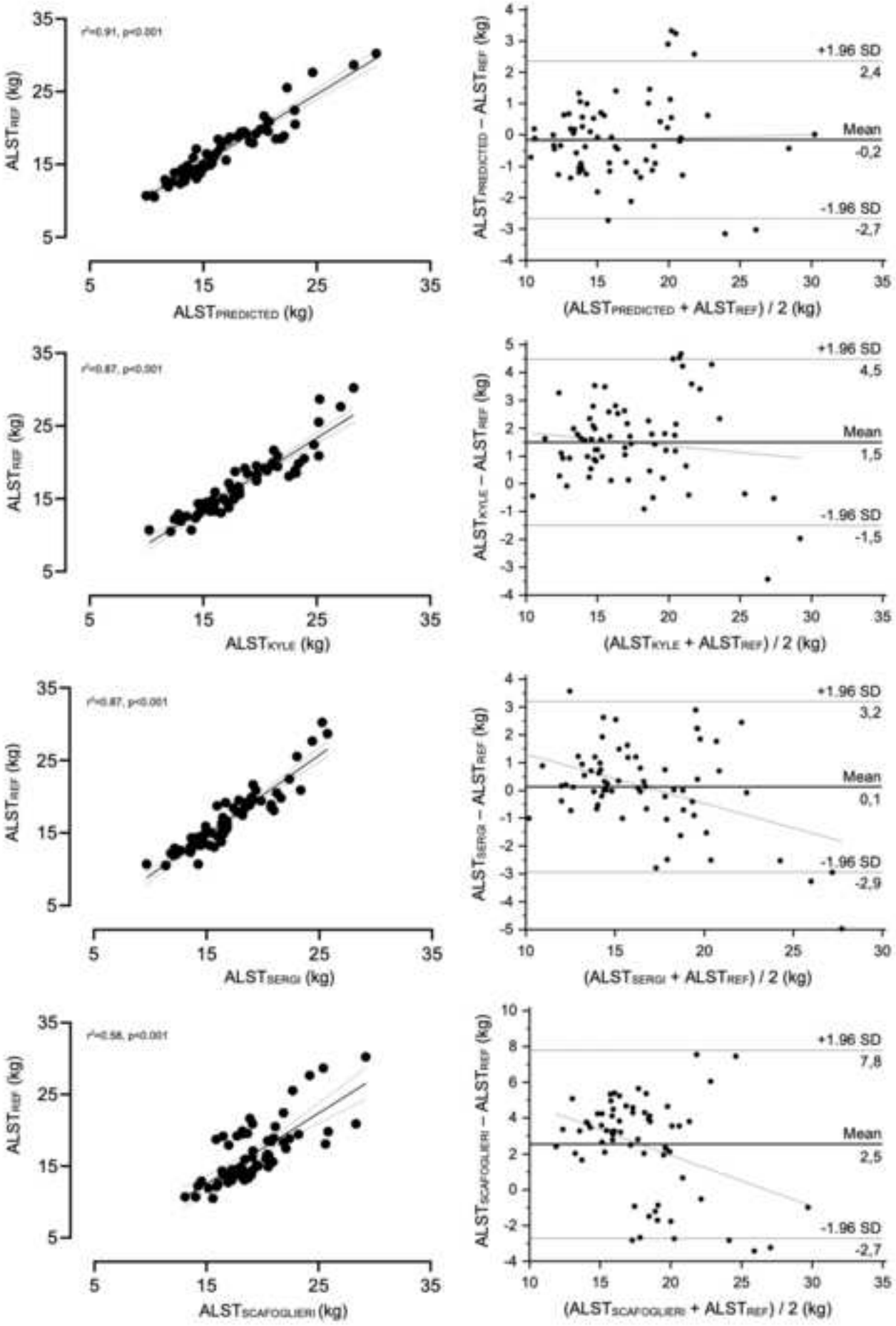

Table 1. Predictive bioelectrical impedance-based equations for appendicular lean soft tissue mass estimation.

Author	Equation	Sample	Age (Years)	BIA-devvice	R^2	SEE
Kyle et al. (2003)	-4.211 + (0.267*S^2/R) + (0.095*Wt) + (1.909*sex[a]) + (-0.012*age) + (0.058*Xc)	113 Healthy men and women	From 22 to 94	Foot-to hand at 50 kHz	0.95	1.12 kg
Sergi et al. (2015)	-3.964 + (0.227*S^2/R) + (0.095*Wt) + (1.384*sex[a]) + (0.064*Xc)	296 Caucasian older healthy male and female adults	71.1 ± 5.6	Foot-to hand at 50 kHz	0.92	1.14 kg
Scafoglieri et al. (2017)	1.821 + (0.168*S^2/R) + (0.132*Wt) + (0.017*Xc) - (1.931*sex[a])	187 Caucasian older male and female adults with functional limitations and sarcopenia	77.0 ± 6.8	Foot-to hand at 50 kHz	0.86	1.37 kg

Abbreviations: S, Stature (cm); R, resistance; Xc, reactance; Wt, body mass; R^2, coefficient of determination; SEE, standard error of estimation. [a] 0 if female; 1 if male.

Table 1. Descriptive characteristics of the development and cross-validation groups (mean ± SD)

Variable	Validation Group (n=118)			Cross-Validation Group (n=66)		
	Men (n=26)	Women (n=92)	Whole group	Men (n=18)	Women (n=48)	Whole group
Age (years)	75.6 ± 7.8	70.9 ± 6.6	71.2 ± 7.2	73.9 ± 7.8	71.3 ± 7.2	72.0 ± 7.4
Weight (kg)	74.3 ± 11.9	67.9 ± 13.2	69.3 ± 13.1	76.2 ± 14.8	67.9 ± 15.7	70.2 ± 15.8
Stature (cm)	166.5 ± 5.2	154.9 ± 6.8	157.5 ± 8.1	167.1 ± 6.4	155.1 ± 6.3	158.4 ± 8.3
Body mass index (kg/m^2)	26.8 ± 3.8	28.3 ± 5.4	27.9 ± 5.1	27.2 ± 4.6	28.2 ± 5.8	27.9 ± 5.5
Waist circumference (mm)	99.6 ± 12.6	93.5 ± 13.0	94.9 ± 14.1	98.7 ± 14.4	93.4 ± 16.0	94.8 ± 15.6
Resistance (ohm)	497.3 ± 60.4	572.4 ± 65.4	555.9 ± 71.3	495.2 ± 66.6	586.7 ± 78.8	561.8 ± 85.7
Reactance (ohm)	46.6 ± 9.4	50.6 ± 8.6	50.3 ± 9.9	45.5 ± 7.6	52.1 ± 10.3	50.3 ± 9.9
Impedance index (m^2/ohm)	56.6 ± 8.1	42.6 ± 6.2	49.7 ± 8.9	57.5 ± 9.7	41.9 ± 7.2	46.2 ± 10.6
Appendicular lean soft tissue mass (kg)	21.3 ± 2.9	14.7 ± 2.0	16.2 ± 3.5	21.5 ± 3.8	14.8 ± 2.4	16.6 ± 4.1
Skeletal muscle index (kg/m^2)	7.7 ± 0.8	6.1 ± 0.7	6.5 ± 0.9	7.7 ± 1.1	6.1 ± 0.8	6.6 ± 1.1

Table 3. Validation of the regression equations for the appendicular lean soft tissue mass estimation.

	ALST	Regression analysis		CCC analysis			Agreement analysis		
	Mean ± SD	r^2	SEE (kg)	CCC	ρ	C_b	Bias	95% LoA	Trend
DXA	16.6 ± 4.1								
Current study	16.5 ± 4.2	0.91	1.27	0.952	0.952	0.999	-0.18	-2.68 , 2.41	r = 0.040, p = 0.750
Kyle et al. (2003)	18.3 ± 3.9 *	0.87	1.53	0.869	0.930	0.934	1.52	-1.51 , 4.48	r = -0.124, p = 0.322
Sergi et al. (2015)	16.8 ± 3.5	0.87	1.53	0.916	0.930	0.984	0.12	-2.93 , 3.20	r = -0.425, p < 0.001
Scafoglieri et al. (2017)	19.2 ± 3.2 *	0.58	2.70	0.598	0.763	0.783	2.48	-2.66 , 7.84	r = -0.368, p = 0.002

Note: ALST, appendicular lean soft tissue; R^2, coefficient of determination; SEE, standard error of estimation; CV, coefficient of variation; CCC, concordance correlation coefficient; ρ, precision; C_b, accuracy; LoA, limits of agreement; DXA, dual-energy x-ray absorptiometry. *= Significant differences with the reference method ($p<0.05$).

Predictive equation for assessing appendicular lean soft tissue mass using bioelectric impedance analysis in older adults: effect of body fat distribution

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Abstract

Background: Low muscle mass is associated with sarcopenia and increased mortality. Muscle mass, especially that of the limbs, is commonly estimated by dual-energy X-ray absorptiometry (DXA) or bioimpedance analysis (BIA). However, BIA-based predictive equations for estimating lean appendicular soft tissue mass (ALST) do not take into account body fat distribution, an important factor influencing DXA and BIA measurements.

Objectives: To develop and cross-validate a BIA-based equation for estimating ALST with DXA as criterion, and to compare our new formula to three previously published models.

Methods: One-hundred eighty-four older adults (140 women and 44 men) (age 71.5 ± 7.3 years, body mass index 27.9 ± 5.3 kg/m^2) were recruited. Participants were randomly split into validation (n=118) and cross-validation groups (n=66). Bioelectrical resistance was obtained with a phase-sensitive 50 kHz BIA device.

Results: A BIA-based model was developed for appendicular lean soft tissue mass [ALST (kg) = 5.982 + (0.188 × S^2/resistance) + (0.014 × waist circumference) + (0.046 × Wt) + (3.881 × sex) – (0.053 × age), where sex is 0 if female or 1 if male, Wt is weight (kg), and S is stature (cm) (R^2=0.86, SEE=1.35 kg)]. Cross validation revealed r^2 of 0.91 and no mean bias. Two of three previously published models showed a trend to significantly overestimate ALST in our sample ($p<0.01$).

Conclusions: The new equation can be considered valid, with no observed bias and trend, thus affording practical means to quantify ALST mass in older adults.

Keywords: Skeletal muscle index, body composition, BIA, elderly, sarcopenia

Key Points:

1. The high cost of imaging techniques precludes their use in most clinical settings.
2. Using a portable, safe, quick, and easy to perform BIA device, our findings provide new valid and non-biased model for appendicular lean soft tissue estimate in older adults.
3. The new model will have practical skeletal muscle index monitoring

Introduction

The prolongation of life expectancy can be observed worldwide as a result of advances in medicine, improvements in public health, economics and social development. Adding the reduction in fertility, the population over 65 is growing faster than any other age group, with forecast to reach 16% of the population in 2050, almost double that in 2019 (Kinsella and Phillips, 2005).

As age advances, major physiological and physical changes in body composition are noticeable. The main ones are reduction of lean mass and increase of fat mass (Campa et al., 2018; Santanasto et al., 2017). The low quantity or quality of muscle associated with a marked reduction in muscle strength represents “sarcopenia”, a progressive skeletal muscle disease, more common in the elderly (Cruz-Jentoft et al., 2019). The excessive increase in body fat, with increasing prevalence among the elderly, is accompanied by ectopic fat accumulation in the muscles (myosteatosis) (Choi et al., 2016). As a result, there is difficulty in neuromuscular activity and contractility of muscle fibers and impaired muscle quality (Choi et al., 2016). For this reason, the link between obesity and sarcopenia is common (Morgan et al., 2020). All changes in body composition observed with advancing age, have a negative impact on the functional capacity of the elderly, generating impairments in mobility and independence, increasing the risk of falls and reducing quality of life (Li et al., 2018). In this sense, muscle quantity and quality are proposed by European Working Group on Sarcopenia in Older People (EWGSOP) 2019 as important factors to be considered to identify sarcopenia (Jiménez-García et al., 2019). Evidence shows that the ageing process is also a determining factor in fat distribution, and waist circumference remains a simple and valid marker of abdominal and visceral fat, providing a highly feasible and inexpensive method to monitor body fat distribution and identify individuals at greater risk of disease in a variety of settings (Stevens et al., 2010). Waist circumference has been positively associated with all-cause mortality in most studies (Cerhan et al., 2014; Pischon et al., 2008) and appears to be strongly associated with multiple chronic diseases (Després et al., 2008).

The dual-energy X-ray absorptiometry (DXA) is commonly used to quantify whole body lean soft tissue mass. By using DXA it is also possible to assess the appendicular lean soft tissue (ALST) mass, and then to calculate the skeletal muscle index (SMI) as the ratio between ALST and the squared stature (SMI=ALST/m^2) (Cruz-Jentoft et al., 2019). The SMI is considered among the EWGSOP 2019 guidelines and it is considered as an index for diagnosing sarcopenia, with reference cut-offs for males and females (Cruz-Jentoft et al., 2019). However, the high cost and low portability hinder the use of DXA in clinical practice. For this purpose, bioelectrical impedance analysis (BIA) is proposed as an alternative method for estimating appendicular lean soft tissue mass using prediction equations. However, the few predictive equations proposed in the literature do not take into account the body fat distribution, a factor that influences the results obtained through these algorithms (Scafoglieri et al., 2017). Furthermore, these formulas all include the bioelectrical value of reactance which differs significantly between the different BIA devices used to evaluate the bioelectrical impedance (Dellinger et al., 2021; Silva et al., 2019). Therefore, the aim of this study was to develop a prediction equation for estimating appendicular lean soft tissue mass considering waist circumference and excluding bioelectrical reactance from the prediction model. Furthermore, the cross validation of the developed model and the performance of the equations present in the literature were evaluated on a separated sample of elderly subjects.

Methods

Design and Settings

The present investigation included older Caucasian adults, aged 60 years or older living in Presidente Prudente (Sao Paulo, Brazil). Research was advertised in the local media and in other places of the municipality with a high concentration of older adults (health centers, social centers, and other social projects). The inclusion criteria consist of being physically independent, ages over 65 years and not taking any type of drugs that may influence the hydration state (e.g., diuretics). From all the older

adults that present in the facilities, 184 (140 women and 44 men) (age 71.5 ± 7.3 years, body weight 69.6 ± 14.1 kg, height 1.57 ± 0.08 m, body mass index 27.9 ± 5.3 kg/m^2) were selected. After receiving detailed information about the purpose of the present study and the possible risks of the investigation, a written consent was filled by all participants. This study was approved by the Ethical Committee at the São Paulo State University (UNESP)/Presidente Prudente (approval code: CAAE 26058114.3.0000.5402).

Body composition

Participants were invited refrain from ingesting food or drink in the previous 4 h, avoid strenuous physical exercise for at least 24h, refrain from the consumption of alcoholic or caffeinated beverages for at least 48 h and avoid the use of diuretics during the seven days preceding collection. The anthropometric traits were weight, height, and waist circumference and were collected by an expert athropometrician. Body height (H) was recorded to the nearest 0.1 cm with a standing stadiometer (Sanny, São Paulo, Brazil) and body mass was measured to the nearest 0.1 kg with a high-precision mechanical scale (Filizola, São Paulo, Brazil). Body mass index (BMI) was calculated as the ratio of body weight to height squared (kg/m^2). Waist circumference was taken to the nearest 0.1 cm (Sanny, São Paulo, Brazil) at the natural waist (in between the lowest rib and the top of the hip bone). The estimation of appendicular lean soft tissue mass was performed using DXA equipment (Lunar brand model DPX-MD, software 4.7) according to the manufacturer protocol. Impedance measurements (resistance, R, reactance, Xc) were obtained using a single-frequency analyzer: the BIA Analyzer (Nutritional Solutions, Harrisville, MI, USA), with a frequency of 50 kHz at 450 µA. According to the standard procedure, whole-body BIA measurements were taken with the participants in a supine position and a leg opening of 45° (Lukaski and Piccoli, 2012). After cleaning the skin with alcohol, four electrodes were placed on the right hand and the right foot. The impedance index was calculated as height (cm) squared divided by R (height^2/R). Skeletal muscle mass index was calculated as the ratio of appendicular lean soft tissue mass to height squared (kg/m^2).

Statistical analysis

Data were analyzed with IBM SPSS Statistics, version 24.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were performed to characterize the sample. All variables were checked for normality, using the Kolmogorov-Smirnov test. Stratified random assignment based on age categories was used to assign participants to either a validation group or a cross validation group. Stepwise regression analysis was used to evaluate the ability of variables to predict appendicular lean soft tissue mass in the validation group. During model development, normality of residuals and homogeneity of variance were tested. The criterion for inclusion of a predictor was to be significant at $p \leq 0.05$. If more than one variable remained in the model, a variance inflation factor (VIF) for each independent variable was calculated and values below five were considered as not having multicollinearity. To cross validate the developed models, the resulting equations were applied to the cross-validation group. A paired sample t-test was used to compare the mean values obtained from the reference technique and from the new method. To assess the accuracy of the new predictive models, validation parameters included the analysis of the concordance correlation coefficient (CCC) calculated with MedCalc Statistical Software v.11.1.1.0, 2009 (MedCalc, Mariakerke, Belgium) was performed. The CCC contains a measurement of precision and accuracy ($\rho c = \rho C_b$): where ρ is the Pearson correlation coefficient, which measures how far each observation deviates from the line of best-fit and is a measure of precision, and C_b is a bias correction factor that measures how far the best fit line deviates from the 45° line through the origin and is a measure of accuracy. Finally, agreement between the developed models and the reference procedure was assessed using the Bland-Altman method, including the analysis of the correlation between the mean and the difference of the methods and an estimate of the limits of agreement. Additionally, the agreement between appendicular lean soft tissue mass estimated in our sample by DXA and the values obtained with the new formula and with that of Kyle (Kyle et al., 2003), Sergi (Sergi et al., 2015), and Scafoglieri (Scafoglieri et al., 2017) was assessed (Table 1).

Insert Table 1 here

Results

Table 2 presents the participants characteristics for the validation and cross validations groups.

Insert Table 2 here

The final developed prediction model for estimating ALST was: ALST (kg) = 5.982 + (0.188 × S^2/resistance) + (0.014 × waist circumference) + (0.046 × Wt) + (3.881 × sex) – (0.053 × age), where sex is 0 if female or 1 if male, Wt is weight (kg), and S is stature (cm) (R^2=0.86, SEE=1.35 kg).

Regarding the regression analysis between DXA approach and the current study developed equations, the methods were highly correlated (r^2 = 0.91; $p < 0.001$), as shown in Table 3 and Figure 1. The precision and accuracy of the methods was higher than 0.95 and 0.99, respectively, with a CCC between the new method and the reference procedure superior to 0.95 (Table 3 and Figure 1). From the agreement analysis, we observed no trend between the mean and the differences of the methods, with limits of agreement considered acceptable. Regarding the preexistent equations available in the literature, while no bias for the Sergi's equation was found, both Kyle and Scafoglieri formulas overestimated ALST measured by DXA in our sample (Table 3 and Figure 1).

*****Insert Table 3 here*****

*****Insert Figure 1*****

Discussion

The purpose of this study was to develop and cross-validate a BIA-based model to predict appendicular lean soft tissue mass using DXA as the criterion method in older people. Furthermore, the main intent was to include a parameter such as waist circumference that would allow taking into account the body fat distribution. In addition, the exclusion of the bioelectrical reactance from the predictive model was desired as it was identified as a bioelectric parameter with a high variability among between-devices comparisons. Then, the predictive model was based on impedance index, waist circumference, weight, sex, and age. The cross-validation procedure showed very strong correlation between the developed equation and the reference method (r^2 = 0.91 at a group level). Moreover, precision and accuracy between the new predictive equation and the reference procedure were analyzed with concordance correlation coefficient analysis (Lin, 1989). In this regard, a moderate strength of agreement between the methods was observed in estimating appendicular lean soft tissue mass. Furthermore, the magnitude of the differences between the new predictive model and the reference method was examined according to the Bland- Altman method (Bland et al., 2012). Therefore, at an individual level, no bias between the mean and the differences of the methods for appendicular lean soft tissue mass was observed and small limits of agreements were presented. Evaluating the appendicular mass allows to calculate the skeletal muscle index, a key parameter in the diagnosis of sarcopenia, nowadays defined as a geriatric syndrome (Cruz-Jentoft et al., 2019; Tallis et al., 2021). The cut-offs indicated in the latest EWGSOP 2019 guidelines propose SMI threshold values of 7.0 and 5.5 kg/m^2 for men and women, respectively (Cruz-Jentoft et al., 2019). In this regard, the use of BIA to estimate appendicular lean soft tissue as an alternative to more accurate methods such as magnetic resonance and DXA, allowing low-cost analysis without the need for expert personnel (B. Heymsfield et al., 1997). In fact, BIA is inexpensive, easy to use, readily reproducible and appropriate for both ambulatory and bedridden patients (Cruz-Jentoft et al., 2010).

When applied to our cross-validation group, the appendicular lean soft tissue mass literature equations (Kyle et al., 2003; Scafoglieri et al., 2017; Sergi et al., 2015) presented a r^2 lower than that assessed

for our new formula, and two of the three considered equations (Kyle and Scafoglieri formulas) showed significant differences between the predictive equation and the reference method and a poor strength of agreement was verified by the CCC analysis. Despite some positive results obtained when the literature equations were applied to our cross-validation group, the mathematical model developed in this investigation presented no mean bias and no trend between methods. In contrast, Sergi and Scafoglieri formulas presented a significant trend in the Bland Altman analysis. Furthermore, Scafoglieri's formula showed a decidedly lower r^2 than the other formulas and this probably because it could be more suitable for sarcopenic subjects such as those included in its development study.

The inclusion of the waist circumference in the equation is justified by its importance in assessing fat distribution in the elderly, whose importance is well known (Alberti et al., 2009; Cerhan et al., 2014; Pischon et al., 2008). In addition, location of body fat impacts DXA soft tissue measures (Valentine et al., 2008) and the outcomes of the predictive equations (Scafoglieri et al., 2017). A positive association between waist circumference and ALST is highlighted in our model. In this regard, Cavedon et al. (Cavedon et al., 2020) showed that in obese females, trunk circumferences are more representative of bodily skeletal muscle than limb circumference even after skinfold correction. They reported that increasing body circumference positively correlates with skeletal muscle mass and strength which are suitable to estimate several such variables. Waist circumference is defined by the IDF worldwide consensus as the criteria for abdominal obesity (Alberti et al., 2009). There is increasing evidence that fat distribution, especially in the abdominal area, is correlated with all-cause mortality (Cerhan et al., 2014; Pischon et al., 2008) and appears to be strongly associated with multiple chronic diseases (Després et al., 2008), such as the most severe state of insulin resistance (IR) (Cheng et al., 2017; Premanath et al., 2014). As an endocrine organ, adipose tissue can secrete free fatty acids and adipocytokines such as tumor necrosis factor-alpha (TNF-α) and leptin, which can interfere with the insulin-signaling system and induce IR (Dodd et al., 2015). Abdominal obesity may also affect bone differently than peripheral subcutaneous fat and potentially affect fracture risk

in elderly (Meyer et al., 2016). Visceral abdominal fat could detrimentally affect bone "quality" (e.g., bone microarchitecture, cortical porosity, bone matrix, mineralization, collagen deposition, geometry, and three-dimensional connectivity of bone) that is independent of bone mineral density (Paik et al., 2019). Avoiding central adiposity as well as maintaining muscle strength may potentially reduce the health risk in older subjects.

Some limitations should be addressed. First of all, this equation may not be applicable to subject affected by diseases or with obesity, as well as subject under the age of 65 years. Secondly, the new model may lose accuracy when applied to BIA devices working at a different frequency than that used in this study. In addition, the use of DXA in the appendicular lean soft tissue mass assessment has been shown to overestimate it when by most accurate imaging techniques such as magnetic resonance and computed tomography, which are considered the gold standards for lean soft tissues assessment (B. Heymsfield et al., 1997). Nevertheless, the use of DXA is considered an acceptable reference technique for assessing body composition in the research context (Sergi et al., 2017). Lastly, the present equation was developed with the use of data from 140 women and 44 men. It is possible that the prediction for men may be compromised as a function of the small number of male subjects involved in this investigation.

Conclusions

The results of this investigation provide a new BIA-based equation for assessing appendicular lean soft tissue mass, for which more sophisticated body composition methods are impractical because of their cost and the time involved. The presented equation is reasonably generalizable for older adults with waist circumference values at the extremes of the distribution, as those involved in this study.

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Figure caption

Figure 1. On the left side the scatterplots with the relationship between the predicted and the reference appendicular lean soft tissue (ALST) mass. On the right side the results of Bland–Altman analyses.