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Development of new adjusted equations to estimate the skeletal muscle mass stratified by nutritional status for patients with rheumatoid arthritis: a methodological study

Desenvolvimento de novas equações ajustadas para estimativa da massa muscular esquelética estratificada pelo estado nutricional para pacientes com artrite reumatoide: um estudo metodológico

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Abstract – Our objective was to adjust and validate predictive equations for appendicular skeletal muscle mass (ASM) in patients with Rheumatoid Arthritis (RA). Whole-body DXA data in 90 RA patients were used for measurement of ASM (kg). The prediction equation anthropometric for muscle mass proposed by Lee et al.was used to generate estimates of ASM. Appendicular skeletal muscle mass index (ASMI, kg/m^2) was calculated. Frequency analysis, Paired student's t-test, Linear regression, Pearson correlation, Intraclass correlation coefficients, and Bland-Altman scatter were performed. The statistical significance considered was p<0.05. Lee's equation was overestimated by 30% when compared with ASMI by DXA. When stratified by nutritional status, Lee's equation overestimated the ASMI by 30% in overweight patients and by 50% in obese patients when compared with DXA (p<0.05). These adjusted equations estimated values for ASMI were closer to those obtained by DXA than those estimated by the original Lee's equation (p<0.05). This greater concordance was confirmed by the observed interclass correlation coefficients and by Bland-Altman scatter graphs. In conclusion, the prediction of muscle mass in RA patients may be performed with equations that consider the nutritional status of patients.

Keywords: Arthritis rheumatoid; Body composition; Anthropometry.

Resumo – *Nosso objetivo foi ajustar e validar equações preditivas para massa muscular esquelética apendicular (ASM) em pacientes com Artrite Reumatoide (AR). Dados de DXA de corpo inteiro em 90 pacientes com AR foram usados para medição de ASM (kg). A equação de predição antropométrica de massa muscular proposta por Lee et al.foi utilizada para gerar estimativas de ASM. Índice de massa muscular esquelética apendicular (ASMI, kg / m2) foi calculada. Análise de frequência, Teste t de Student pareado, Regressão linear, Correlação de Pearson, Coeficientes de correlação intraclasse e Dispersão de Bland-Altman foram realizados. A significância estatística considerada foi p<0,05. A equação de Lee superestimou em 30% quando comparada com a ASMI da DXA. Quando estratificada por estado nutricional, a equação de Lee superestimou o ASMI em 30% em pacientes com sobrepeso e em 50% em pacientes obesos em comparação com DXA (p<0,05). Esses valores estimados de equações ajustadas para ASMI foram mais próximos daqueles obtidos por DXA do que aqueles estimados pela equação de Lee original (p<0,05). Essa maior concordância foi confirmada pelos coeficientes de correlação interclasses observados e pelos gráficos de dispersão de Bland-Altman. Em conclusão, a predição da massa muscular em pacientes com AR pode ser realizada com equações que consideram o estado nutricional dos pacientes.*

Palavras-chave: *Artrite reumatoide; Composição corporal; Antropometria.*

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INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic, progressive, inflammatory autoimmune disease characterized by systemic manifestations[1,2]. Changes in body composition are observed in RA patients as reduced fat-free mass, especially appendicular skeletal mass, with stable or increased fat mass[3-5]. These alterations are related to the chronic inflammatory state[4,6].

Body composition assessment, particularly appendicular skeletal mass, is a key component of the evaluation of the health and functional status of older adults[7]. Appendicular skeletal muscle (ASM) is the most parameter for the assessment of geriatric syndromes associated with skeletal muscle wasting, such as sarcopenia and geriatric cachexia[8].

Estimation of appendicular skeletal muscle mass *in vivo* can be accomplished by a variety of methods, such as Dual-energy X-ray absorptiometry (DXA), Computed tomography (CT), Magnetic resonance imaging (MRI), and Bioelectrical impedance analysis (BIA)[8-10]. These modalities are considered the gold standard for this purpose; however, their high cost makes their use unfeasible in population studies and increases the difficulty of use in different clinical contexts.

Predictive equations have been developed for the estimation of appendicular skeletal muscle mass as the basis of anthropometric data[11], which can be collected in a more affordable manner, in an attempt to make muscle mass estimation easier and enable its use in epidemiological research and clinical settings[11]. However, these equations have not been validated or adjusted for specific populations, such as in RA patients, which may present differences in muscle and fat body composition from normal individuals. Therefore, the purposes of this study were: (1) to adjust predictive equations for ASMI and (2) to validate the adjusted predictive equations for ASMI by nutritional status in patients with RA.

METHOD

Sample

This study utilized whole-body DXA data at baseline from Santo et al.[12] of the adults diagnosed with RA. Santo et al.[12] conducted a cohort study at Hospital de Clínicas de Porto Alegre in patients with RA of 2015 until this moment. This cohort study received Institutional Review Board (IRB) approval of *Hospital de Clínicas de Porto Alegre* (Brazil) and is registered under number 30070320.4.0000.5327. All the patients signed an informed consent form.

In this study, the sample was distributed by two different groups: the adjustment group (70% of the sample data) and the validation group (30% of the sample data). Adjustment groups were used (1) to assess the appendicular skeletal mass index (ASMI) assessed by DXA and anthropometric prediction equation, (2) to compare to ASMI assessed by DXA with anthropometric prediction equation, and (3) to develop new adjusted anthropometric equations by nutritional status. A validation group was used to validate the anthropometric equations developed.

Body composition assessment

Body composition was evaluated by dual-energy X-ray absorptiometry (DXA; Lunar Prodigy Primo, GE Medical Systems). Whole-body DXA was performed to estimate appendicular skeletal muscle mass (ASM, kg). The appendicular skeletal muscle mass index (ASMI) was determined by the sum of arm muscles and leg muscles and dividing the respective estimate by height squared (ASM/height^2). The variation coefficients of The Lunar Prodigy Primo, GE Medical Systems are: 520g to fat mass, 610g to lean mass, and 210g to total body weight.

Anthropometric measures

Bodyweight was measured on an anthropometric scale with a resolution of 100g (Filizola S.A. Pesagem e Automação, São Paulo, Brazil). Height, age, and race data were collected by a review of medical records. Nutritional status was assessed by body mass index (BMI). The BMI was calculated as weight divided by height squared, expressed in kg/m^2, adjusted for age, and categorized as according to the definition of the World Health Organization (WHO) for adults: underweight (<18.5 kg/m^2), normal weight (18.5–< 25 kg/m^2), overweight (25–< 30 kg/m^2) and obese (≥30 kg/m^2)[13].

Anthropometric predictive equation

The anthropometric predictive equation for estimation the skeletal muscle mass was applied using the variables: body weight, weight, age, gender, and race[11]. The equation is presented below:

Skeletal muscle mass predictive equation proposed by Lee et al.[11]:

$$ASM\ (kg) = (0.244x\ body\ weight) + (7.80\ x\ height) - (0.098\ x\ age) + (6.6\ x\ sex) + race - 3.3 \quad (1)$$

Statistical analysis

The statistical analysis was divided into two phases to achieve the objective of this study: Phase 1 and 2.

Phase 1: Mean and standard deviation were used to describe the ASM by DXA and ASM by anthropometric measures of the sample. The paired student's T-test was used to compare the appendicular skeletal mass (ASM) and the appendicular skeletal mass index (ASMI) assessed by DXA with an anthropometric prediction equation. Given the existence of significant differences between methods, we hypothesized that being overweight or obese may have an impact on the estimates with Lee's equation. Thus, multiple linear regression analyses with variables of anthropometric equation (body weight, weight, age, gender, and race) and stratified by nutritional status were performed. New values for the constants on equations were calculated and new equations for estimation ASMI stratified by nutritional status were constructed. Pearson correlation was used to assess the correlation among DXA data, anthropometric prediction equation, and the adjusted predictive equations by nutritional status. All analysis was considered significant statistical when $p<0.05$;

Phase 2: The independent-samples t-test was performed to validate the adjusted predictive equations by nutritional status. Interclass correlation coefficients (ICC) and a Bland-Altman plot graphically were calculated and used to assess the agreement between ASM estimates by DXA and by the predictive equations. The significance level was set at $p \leq 0.05$ for all analyses. Statistical analyses were performed in PASW 18.0 Statistics for Windows.

RESULTS

Table 1 summarized the characteristics of the RA patients included in the cohort study[12]. From this whole-body DXA data of the cohort study[12], we assessed the appendicular skeletal muscle mass (ASM) and the appendicular skeletal muscle mass index (ASMI). In addition, we estimated the ASMI by the predictive equation of Lee et al.[11]

The ASM by DXA showed a mean of 17.0±3.7 kg and the ASM by the predictive equation of Lee et al.[11] showed a mean of 22.0±5.2 kg (p=0.000). In addition, the ASMI by DXA showed a mean of 6.6±0.94 kg/m^2 and the ASM by the predictive equation of Lee et al.[11] showed a mean of 8.6±1.54 kg/m^2 (p=0.000). Thus, Lee's equation overestimated 29.4% of the ASM and 30.0% of the ASMI when compared with that estimated by DXA.

We hypothesized that being overweight or obese may have an impact on the estimates with Lee's equation[11]. Therefore, the linear regression was performed with the same variables included on the predictive equation of Lee et al.(body weight, height, age, gender, and race), however, categorized by nutritional status (normal weight, overweight and obese). Thus, the new values for the constants on equations were calculated and three new adjusted equations (normal weight, overweight and obese) for estimation ASM stratified by nutritional status were constructed:

$$Normal\ weight\ (BMI \leq 18{,}5\ and\ < 25): ASM\ (kg) = (0.116\ x\ body\ weight) + (14.94\ x\ height) - (0.027\ x\ age) + (6.64\ x\ sex) - (0.611x\ race) - 13.45; \quad (2)$$

$$Overweight\ (BMI \geq 25\ and\ < 30): ASM\ (kg) = (0.177\ x\ body\ weight) + (7.61\ x\ height) - (0.011\ x\ age) + (5.18\ x\ sex) + (0.211x\ race) - 9.08 \quad (3);$$

$$Obese\ (BMI \geq 30): ASM\ (kg) = (0.058\ x\ body\ weight) + (13.84\ x\ height) - (0.087\ x\ age) + (5.07\ x\ sex) + (0.702\ x\ race) - 5.04) \quad (4).$$

With 70% (n=63) of data of cohort study[12] at baseline, we constructed adjusted equations for estimation of ASM stratified by nutritional status, as described in the Methods section. In fact, when stratified by nutritional status, Lee's equation overestimated the ASMI by 31% in overweight patients and by 50% in obese patients when compared with DXA ($p<0.05$), while that, the three new adjusted equations (normal weight, overweight and obese) for estimation ASM stratified by nutritional status did not overestimate ASMI when compared with DXA ($p<0.05$; Table 2).

In addition, the three new adjusted equations (normal weight, overweight and obese) for estimation ASM stratified by nutritional status showed stronger correlations with DXA (normal weight: r=0.913; overweight: r=0.908; obese: r=0.924; $p<0.01$) when compared with analysis between Lee equation and DXA (r=0,842; $p<0.01$). Subsequently, we validated the adjusted equations for ASM estimation stratified by nutritional status applying them in the remaining 30% (n=27) data of cohort study[12] at baseline. These adjusted equations estimated

values for ASM closer to those obtained by DXA than those estimated by the original Lee's equation (Table 3). This greater concordance was confirmed by the observed interclass correlation coefficients (ICC) (Table 4), as well as by Bland-Altman scatter graphs (Figure 1). These graphs plot the difference between the DXA and the various equations estimates for ASM against the average of these two estimates. The solid line shows the mean of the differences, while the dashed lines, the lower and upper limits (± 2DP). We may observe that the mean difference between DXA and Lee's equation estimates was -2,0kg (p=0.000) indicating that these two measurements have a significant statistical difference, with a trend for higher differences in patients with higher ASM (Figure 1A). On other hand, the mean differences between DXA and the estimates from the adjusted equations by nutritional status were 0,02 kg (p=0.810) (Figure 1B), -0,28 kg (p=0.767) (Figure 1C), and -0,63 (p=0.948) (Figure 1D), for the normal weight, overweight and obese patients, respectively, indicating that there is not a significant statistical difference and therefore a very good concordance.

Table 1. Demographic and clinical characteristics of the study sample.

	n=90
Age (years old), mean ± SD	56.5±7.3
Disease duration (years), median (IQR)	8.5 (3.0-18.0)
Women, n (%)	78 (86.7)
Men, n (%)	12 (13.3)
Caucasian, n (%)	62 (68.9)
Current smoker, n (%)	18 (20.0)
Rheumatoid factor positive, n (%)	77 (85.6)
Disease activity	
DAS-28–CRP, median (IQR)	3.0 (1.0-3.0)
Remission (DAS-28–CRP <2.3), n (%)	25 (27.8)
Low disease activity (2.3> DAS-28–CRP <2.7), n (%)	8 (8.9)
Moderate disease activity (2.7> DAS-28–CRP <4.1), n (%)	31 (34.4)
High disease activity (DAS-28–CRP >4.1), n (%)	19 (21.1)
Treatment regimen	
MTX monotherapy, n (%)	52 (57.8)
MTX with concurrent csDMARD,n (%)	14 (100.0)
MTX dose (mg/week), median (IQR)	20.0 (15.0-25.0)
bDMARDs, n (%)	27 (30.0)
Glucocorticoids, n (%)	53 (58.9)
Glucocorticoid dose (mg/day), median (IQR)	5.0 (5.0-10.0)

Note. DAS-28–CRP, the Disease Activity Score-28 with C reactive protein; MTX, Methotrexate; csDMARD (conventional synthetic disease-modifying antirheumatic drugs): methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine; bDMARDs (biologic disease- modifying antirheumatic drugs): adalimumab, etanercept, infliximab, certolizumab, golimumab, rituximab, tocilizumab, abatacept.

Table 2. Comparison among ASMI assessed by DXA, skeletal muscle mass predictive equation proposed by Lee et al.[12] and the adjusted equations for estimation skeletal muscle mass stratified by nutritional status.

	ASMI (DXA)	ASMI (Lee equation)	The adjusted equations for estimation ASMI are stratified by nutritional status.
Normal weight (BMI ≤18,5 and < 25); (n=24), mean ± SD	6.03±0.71	7.14±0.85	6.04±0.58
Overweight (BMI ≥25 and < 30); (n=32), mean ± SD	6.57±0.82	8.63±0.99*	6.58±0.83
Obese (BMI ≥30); (n=13), mean ± SD	7.10±0.73	10.66±1.19*	7.10±0.57

Note. *Paired student's t-test; p≤0.05.; BMI, Body Mass Index; ASM, Appendicular skeletal muscle mass.

Table 3. The validation of the adjusted equations for estimation ASMI stratified by nutritional status using 30% of the data from an ongoing prospective study in a cohort of patients with RA.

	ASMI (DXA)	ASMI (Lee equation)	The adjusted equations for estimation ASMI are stratified by nutritional status.
Normal weight (BMI ≤18,5 and < 25); (n=8), mean ± SD	6.50±1.29	7.48±1.13	6.43±1.05
Overweight (BMI ≥25 and < 30); (n=10), mean ± SD	6.68±0.70	8.71±0.87*	6.71±0.73
Obese (BMI ≥30); (n=8), mean ± SD	6.94±0.58	10.05±1.09*	6.92±0.27

Note. *Paired student's t-test; p≤0.05., BMI, Body Mass Index; ASM, Appendicular skeletal muscle mass.

Table 4. The intraclass correlation coefficient (ICC) among ASMI assessed by DXA, Lee equation, and the adjusted equations for estimation ASMI stratified by nutritional status

	Lee's equation x DXA	Lee equation x DXA	The adjusted equations for estimation ASM are stratified by nutritional status.
Normal weight (BMI ≤18,5 and <25)	0.78 (0.66-0.85)*	0.87 (0.72-0.94)	0.95 (0.9-0.97)
Overweight (BMI ≥25 and < 30):		0.83 (0.68-0.91)	0.85 (0.74-0.93)
Obese (BMI ≥30):		0.77 (0.42-0.90)	0.87 (0.68-0.95)

Note. *Included all patients without stratified by BMI; ASM, Appendicular skeletal muscle mass.

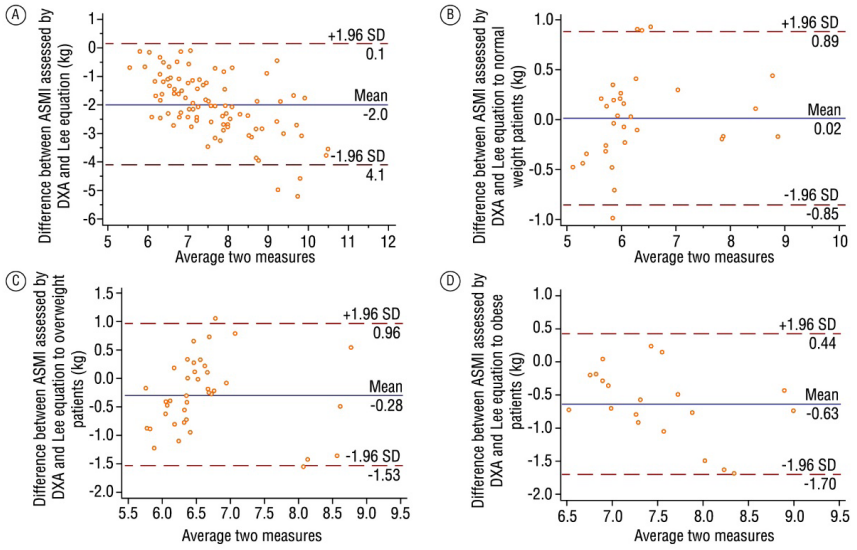

Figure 1. The Bland-Altman graphs. Differences between DXA and Lee equation (A); Difference between DXA vs adjusted equation for estimation ASM in normal weight (B); Difference between DXA vs adjusted equation for estimation ASM in overweight (C); Difference between DXA vs adjusted equation for estimation ASM in obese (D), are all plotted against the average of the DXA and equation measures.

DISCUSSION

The main finding of this study was that the adjusted equations for estimation of the appendicular skeletal mass (ASM) stratified by nutritional status demonstrated more concordant predictions with DXA values than the original Lee's equation[11] in RA patients. In addition, the muscle mass index by Lee's equation overestimates the muscle mass in overweight and obese RA patients compared to DXA. To the best of our knowledge, this was the first study to compare anthropometric equations that estimate ASMI with that derived

from DXA to construct the adjusted equations for estimation ASM stratified by nutritional status for rheumatoid arthritis patients.

Currently, Dual-energy X-ray absorptiometry (DXA), an instrument non-invasively, is used by some clinicians and researchers for measuring muscle mass[9]. However, DXA has a high cost, is not a reality in healthcare in low- and middle-income countries, and is not liable to be carried out in all healthcare scenarios, such as in primary care and low complexity clinics. Thus, having estimates based on anthropometric measures that are easy to use and reliable predictors of muscle mass are important for screening patients with low muscle mass and proposing prevention strategies.

The idea of using anthropometrical methods to assess body composition is not recent. In 1921, Matiegka[14] suggested an anthropometric approach for quantifying whole-body composition. More recently, studies extended Matiegka's[14] approach and developed anthropometric ASM prediction formulas based on the Brussels Cadaver Study[15-19]. In 2000, Lee et al.[11] proposed the predictive equations for estimation of ASM in healthy adults using Magnetic resonance imaging (MRI) as a comparison standard. The subjects were then divided into 2 groups, no obese [body mass index (BMI; in kg/m^2) < 30] and obese (BMI≥30). The anthropometric prediction equation was developed with body weight (BW); (in kg) and height (in meters) as the major predictors. The other independent variables included were age, gender, and race. This model had good prediction qualities. However, the authors described that a small bias occurred when the model was cross-validated in the no obese subjects and the obese subjects. The predicted group mean ASM was significantly larger (10%) than that measured for the obese group. Hence, Lee et al.[11] described that this model should not be applied in obese subjects. Therefore, nutritional status should be a controlled variable, as it can influence the results of ASM prediction, especially in overweight patients or those with chronic inflammatory diseases that do not alter the body weight.

Although the original Lee's equation[11] had been validated in 180 Brazilian older adults (120 women and 60 men) aged 60 to 81 years[19], our findings demonstrated that in overweight and obese patients with chronic inflammation as RA patients, the original Lee's equation[11] did not reproduce the ASM. In our patients, the original Lee's equation[11] overestimated in 30% the ASM when compared with that estimated by DXA. Thus, sarcopenic RA patients may be wrongly classified as having normal muscle mass by the equation. Considering that RA patients show reduced fat-free mass, especially appendicular skeletal mass, with stable or increased fat mass, but may not experience significant weight loss and may maintain a normal body mass index (BMI)[4,5,20], we speculated that its necessary to take into account nutritional status for RA population. The discrepancy between the equation and DXA estimations was not observed when the equation was adjusted according to nutritional status. The estimates of the adjusted equations were similar and concordant to the values measured by DXA in RA and confirmed by Bland-Altman scatter graphs.

The present study presented as the main limitation the small sample size. Therefore, it is necessary to assess these adjusted equations for ASM in a larger population of RA patients, particularly testing with more men and different age groups. In addition, the cross-sectional design and the fact that we used a specific RA population (tertiary center with high rates of moderate-to-severe

activity measured by composite indexes and a great proportion of patients on bDMARD) also is a limitation.

CONCLUSION

In conclusion, this study suggests that the prediction of appendicular skeletal mass in RA patients can be performed with equations that consider the patients' nutritional status. Cohort studies are needed to better assess the equations proposed in this study and risk factors to changes in body composition observed in RA patients.

COMPLIANCE WITH ETHICAL STANDARDS

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Ethical approval

Ethical approval was obtained from the local Human Research Ethics Committee –Hospital de Clínicas de Porto Alegre and the protocol (no. 2015-0297) was written following the standards set by the Declaration of Helsinki.

Conflict of interest statement

The authors have no conflict of interests to declare.

Author Contributions

Conceived and designed the experiments: Espírito Santo RC, Filippin LI, Lora PS, Xavier RM; Performed the experiments: Espírito Santo RC. Analyzed the data: Espírito Santo RC, Filippin LI, Lora PS, Xavier RM; Contributed reagents/materials/analysis tools: Espírito Santo RC, Filippin LI, Lora PS, Xavier RM; Wrote the paper: Espírito Santo RC, Filippin LI, Lora PS, Xavier RM.

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