

Characteristics of Appendicular Tissue Components in Patients with Rheumatoid Arthritis

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Background: The purpose of this study was to identify the characteristics of appendicular lean mass (ALM) associated with rheumatoid arthritis (RA) and to analyze appendicular tissue components in patients with RA. **Methods:** We prospectively reviewed of patients with RA who underwent dual energy X-ray absorptiometry in a single center. From data of 28 patients, ALM was calculated. Regression analysis was used to investigate the association between ALM and RA. Using propensity score matching, patients with RA were compared to the control group from 18,698 patients of Korea National Health and Nutrition Examination Surveys data. RA and control group were matched in a 1: 5, respectively. **Results:** In regression model, there was significantly negative association between disease activity score and ALM index in patients with RA in unadjusted ($\beta = -0.387$, 95% confidence interval [CI], -0.729 to -0.045) and model adjusted for age, sex, and body mass index ($\beta = -0.227$, 95% CI, -0.451 to -0.003). In matching with age and sex, the arms fat mass and fat fraction of RA group were significantly lower than that of control group. In matching with age, sex, and body mass index, the ALM index and legs lean mass of RA group were significantly higher than control group. **Conclusions:** Patients with RA have a lower ALM with higher disease activity. In addition, we found that patients with RA had different tissue component in arms and legs compared to general population.

Key Words: Adiposity · Arthritis, rheumatoid · Body composition

INTRODUCTION

Sarcopenia is related to daily life disability, and is an independent risk factor of falls in older people, and premature mortality.[1,2] It is mainly observed in older people, but it can also appear in younger adults in the course of many clinical conditions.[3] In patients with rheumatoid arthritis (RA), decrease of muscle mass have been observed in studies.[4,5] The main causes of lean body mass decrease in the course of RA are chronic inflammation accompanying the disease, decrease in physical activity, chronic pain, and increase of energy expenditure during rest.[6]

Patients with RA were also associated with risk of overfat and obesity.[5,7] In addition, adiposity is important confounder in estimating muscle mass because there is a strong positive association between skeletal muscle mass and fat mass.[8,9] Baker et al. [4] estimated the appendicular lean mass (ALM) adjusting for adiposity. They suggested that increasing fat mass was associated with disability and strong associations between ALM and functional outcomes. Therefore, not only muscle

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mass but also fat mass assessment is important to analyze appendicular tissue component of patients with RA.

The purpose of this study is to find significant factors related to ALM in patients with RA and determine difference of appendicular tissue component between patients with RA and general population.

METHODS

1. Study design and participants

We prospectively collected patient's data between March 2018 and February 2019 in a single center. Patients previously diagnosed with RA according to the 2010 RA classification criteria [10] and underwent dual energy X-ray ab-

sorptiometry (DXA) were included. The Inje University Seoul Hospital institutional review board approved this study (PAIK 2018-04-003). Informed consent was obtained from all RA patients included in the study.

Clinical characteristics including age, sex, body mass index (BMI), rheumatoid factor, anti-cyclic citrullinated peptide antibody, disease activity score (DAS) 28,[11] current medication including glucocorticoid, disease modifying anti-rheumatic drugs, biologics, osteoporosis medication. All patients underwent DXA. Bone mineral density (BMD) was obtained at lumbar spine and one proximal femoral area (Lunar Prodigy Advance; GE Lunar, Madison, WI, USA). T-score at total spine, total femur, femur neck was measured. From the report of soft tissue content, we obtained

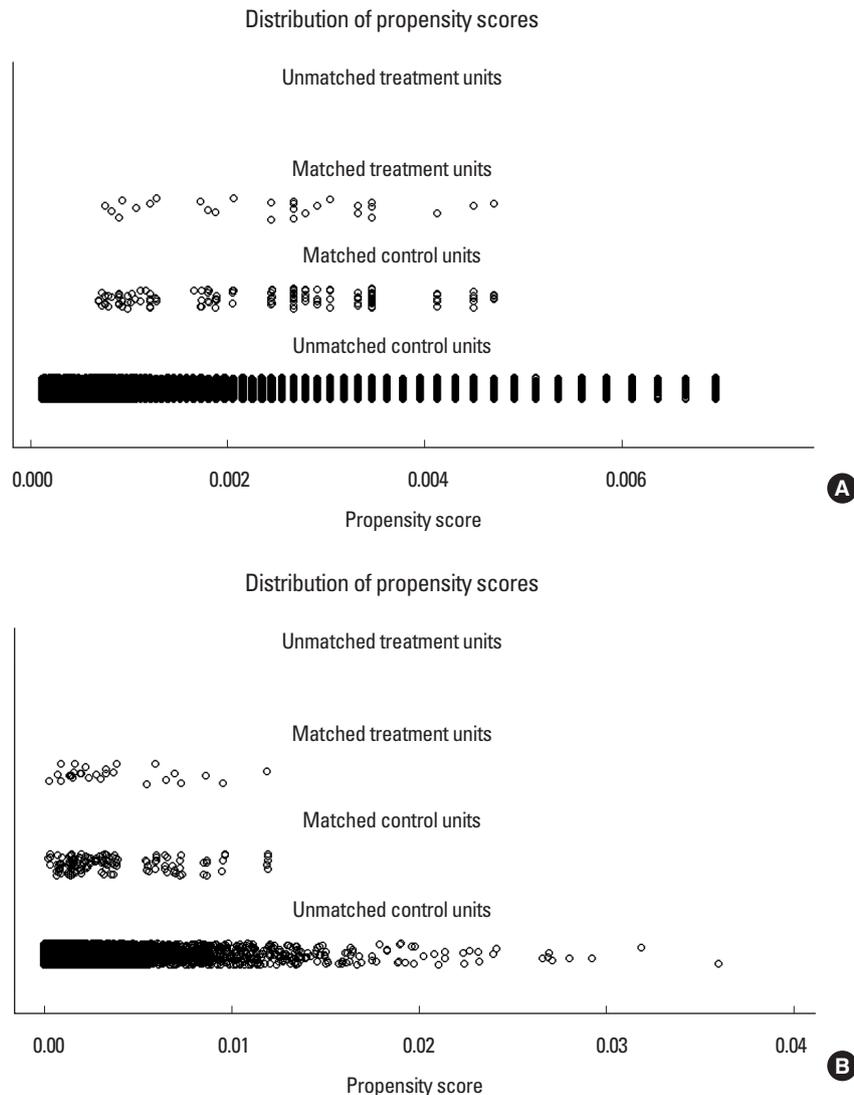


Fig. 1. Nearest neighbor propensity score matching (A) with age, sex and (B) with age, sex, and body mass index.

fat and lean mass (kg) of arms and legs. Using the information, we calculated fat fraction of soft tissue (%) and ALM index ($ALM/height^2$). Adjusted criteria considering Asian low muscle volume were conducted for sarcopenia (male $<7.00\text{ kg/m}^2$, female $<5.40\text{ kg/m}^2$).[12]

2. Definition of control group

We used data of the Korea National Health and Nutrition Examination Survey (KNHANES) as control group. This nationally representative cross-sectional survey includes approximately 10,000 individuals each year as a survey sam-

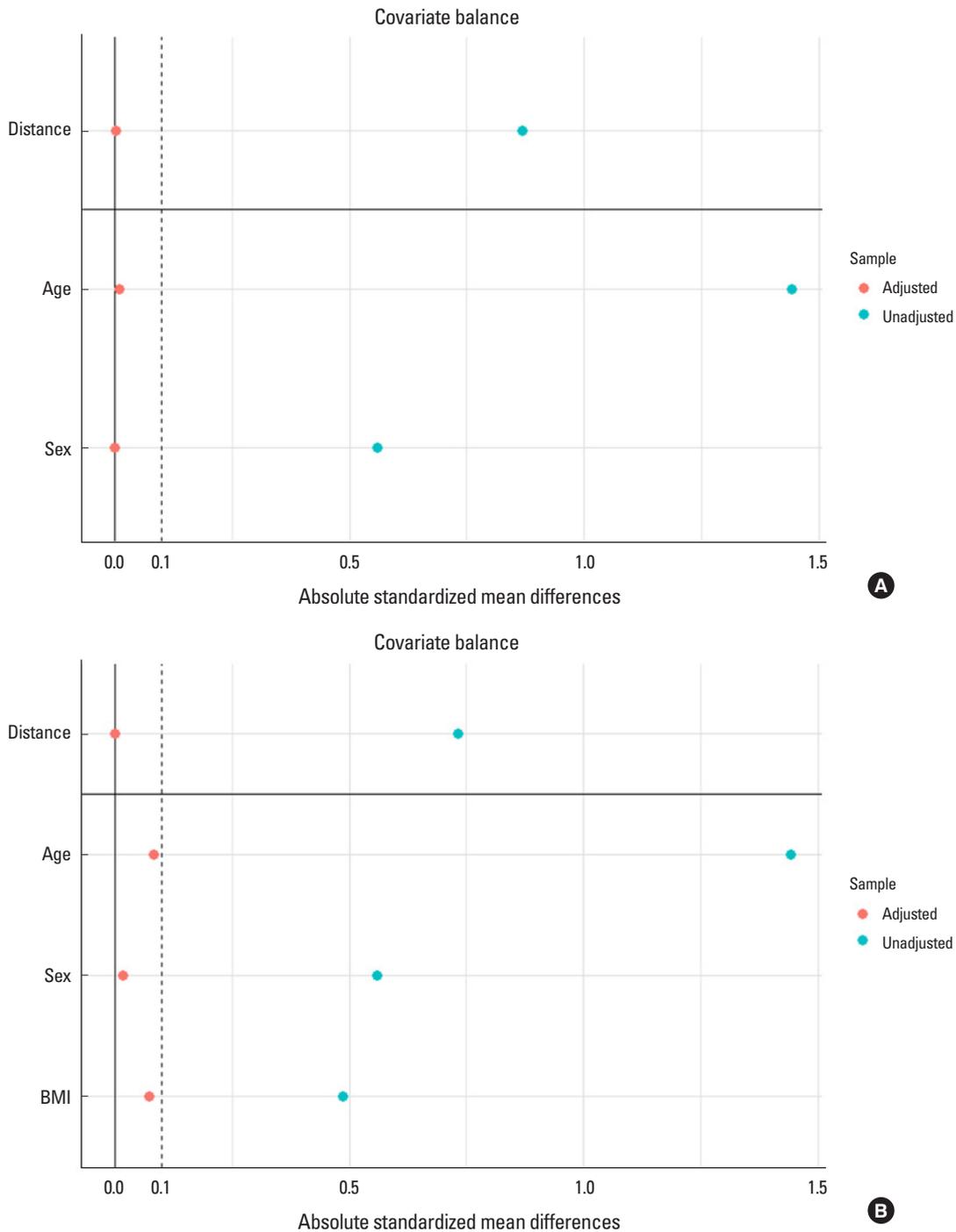


Fig. 2. Absolute standardized mean difference of matching (A) with age, sex and (B) with age, sex, and body mass index. The dashed line is standardized mean difference 0.1.

ple and collects information on socioeconomic status, health-related behaviours, quality of life, healthcare utilization, anthropometric measures, biochemical and clinical profiles for non-communicable diseases and dietary intakes with 3 component surveys.[13] In the data, appendicular tissue mass including fat and lean mass and BMD measured with DXA (QDR 4500A; Hologic Inc., Bedford, MA, USA) were obtained for 2008 to 2011. We extract data of age, sex, BMI, fat and lean mass, BMD from KNHANES data. We obtained control group of 18,698 individuals.

3. Statistical analysis

Clinical characteristics of patients with RA was shown as mean with standard deviation (SD) or median with interquartile range (IQR). We used the linear regression to assess the association between ALM index and variables in patients with RA. We also calculated the β coefficients adjusting age, sex, and BMI. Using RA and control group, a nearest-neighbor propensity score matching was conducted in a 1:5 using a 0.05 caliper (Fig. 1). We created 2 model; model 1 matching variables with age and sex and model 2 matching variables with age, sex, and BMI. The absolute standardized mean differences of the variables used for matching were all less than 0.1 (Fig. 2). The Pearson χ^2 test or Fisher's exact test was used for categorical variables. After normality was tested using the Shapiro-Wilk test, the Student *t*-test or the Mann-Whitney *U* test for continuous variables were used for comparison between groups. All *P* values of less than 0.05 were assumed to indicate statistical significance. All statistical analyses were performed with R (version 3.6.0; The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

1. Baseline clinical characteristics

Table 1 summarizes the clinical characteristics of patients with RA. The mean age was 58.5 ± 8.9 years. The proportion of female was 78.6%. The mean BMI was 21.8 ± 3.2 kg/m². In most patients, erythrocyte sedimentation rate ($24.5 [11.0; 50.0]$ mm³/hr) and C-reactive protein (CRP; $0.2 [0.2; 0.6]$ mg/dL) did not indicate high inflammation. The mean DAS 28 was 2.3 ± 1.0 with remission status. The 17, 8, and 3 patients were in remission, low disease activity and moderate disease activity, respectively. Health assessment question-

Table 1. Baseline characteristics of patients with rheumatoid arthritis

	Rheumatoid arthritis (n=28)
Age (yr)	58.54 ± 8.9
Female	22 (78.6)
BMI (kg/m ²)	21.8 ± 3.2
Disease duration (year)	8.3 ± 5.6
Rheumatoid factor	21 (75.0)
Anti-CCP	21 (75.0)
ESR (mm ³ /hr)	24.5 (11.0 to 50.0)
CRP (mg/dL)	0.2 (0.2 to 0.6)
DAS28	2.3 ± 1.0
HAQ score	0.1 (0.1 to 0.2)
Glucocorticoid	7 (25.0)
DMARDs	27 (96.4)
Biologics	8 (28.6)
Osteoporosis medication	4 (14.3)
T-score	
Total spine	-1.0 ± 1.5
Femur neck	-1.2 ± 1.0
Total femur	-1.0 ± 1.2
Arms	
Fat mass	1.7 ± 0.8
Lean mass	3.5 (3.1 to 4.3)
Fat fraction (%) ^{a)}	30.5 ± 11.9
Legs	
Fat mass (kg)	5.7 ± 2.6
Lean mass (kg)	12.6 ± 2.7
Fat fraction (%) ^{a)}	30.6 ± 11.0
ALM index (kg/m ²)	6.3 ± 1.0
Sarcopenia	6 (21.4)

The data is presented as mean ± standard deviation, median (interquartile range), or number (%).

^{a)}The percentage of fat mass in total tissue mass.

BMI, body mass index; CCP, cyclic citrullinated peptide; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28, disease activity score 28; HAQ, health assessment questionnaire; DMARDs, disease-modifying anti-rheumatic drugs; ALM, appendicular lean mass.

naire (HAQ) score was 0.1 (0.1; 0.2) with very low value. Most patients (96.4%) were treated with disease-modifying antirheumatic drug and 28.6% were treated with biologics. The mean BMD of spine and femur showed osteopenia and there were 15 and 5 patients diagnosed with osteopenia and osteoporosis, respectively. The mean fat fraction of arms and legs was 30.5 ± 11.9 kg and 30.6 ± 11.0 kg, respectively. The mean ALM index was 6.3 ± 1.0 kg/m² and 6 patients (21.4%) were classified as sarcopenia in patients with RA.

Table 2. The association between appendicular lean mass index and other variables in patients with rheumatoid arthritis (n=28)

	Unadjusted model		Adjusted model ^{a)}	
	Coefficient (95% CI)	P-value	Coefficient (95% CI)	P-value
Age	0.001 (-0.043 to 0.044)	0.979		
Female	-1.575 (-2.246 to -0.903)	<0.001		
BMI	0.101 (-0.011 to 0.213)	0.075		
Disease duration	-0.069 (-0.133 to -0.006)	0.033	-0.037 (-0.089 to 0.015)	0.158
Rheumatoid factor	-0.252 (-1.122 to 0.618)	0.556	0.273 (-0.298 to 0.844)	0.334
Anti-CCP	0.277 (-0.592 to 1.146)	0.518	0.102 (-0.449 to 0.653)	0.705
Log (ESR)	-0.289 (-0.645 to -0.068)	0.108	-0.137 (-0.379 to 0.105)	0.254
Log (CRP)	-0.117 (-0.491 to 0.257)	0.525	-0.085 (-0.319 to 0.149)	0.459
DAS28	-0.387 (-0.729 to -0.045)	0.028	-0.227 (-0.451 to -0.003)	0.047
Log (HAQ)	-0.691 (-1.222 to -0.159)	0.013	-0.510 (-0.826 to -0.193)	0.003
Glucocorticoid	-0.797 (-1.612 to 0.018)	0.055	-0.290 (-0.857 to 0.276)	0.300
DMARDs	-0.876 (-2.888 to 1.137)	0.379	-0.777 (-2.086 to 0.532)	0.232
Biologics	-0.3217 (-1.151 to 0.5077)	0.432	-0.032 (-0.573 to 0.508)	0.903
Osteoporosis medication	-0.299 (-1.376 to 0.778)	0.574	0.660 (-0.054 to 1.373)	0.068
T-score				
Total spine	0.078 (-0.174 to 0.330)	0.531	-0.136 (-0.304 to 0.033)	0.110
Femur neck	0.111 (-0.257 to 0.479)	0.542	-0.223 (-0.476 to 0.031)	0.082
Total femur	0.349 (0.047 to 0.651)	0.025	-0.059 (-0.342 to 0.225)	0.673
Arms				
Fat mass	-0.075 (-0.538 to 0.388)	0.741	-0.361 (-0.944 to 0.221)	0.213
Lean mass	0.837 (0.621 to 1.052)	<0.001	0.738 (0.202 to 1.275)	0.009
Fat fraction ^{b)}	-0.034 (-0.064 to -0.005)	0.024	-0.049 (-0.086 to -0.012)	0.011
Legs				
Fat mass	-0.043 (-0.190 to 0.104)	0.553	0.007 (-0.173 to 0.187)	0.937
Lean mass	0.331 (0.276 to 0.386)	<0.001	0.333 (0.240 to 0.426)	<0.001
Fat fraction ^{b)}	-0.043 (-0.073 to -0.012)	0.008	-0.051 (-0.096 to -0.007)	0.025

^{a)}Adjusted with age, sex, and body mass index. ^{b)}The percentage of fat mass in total tissue mass.

CI, confidence interval; BMI, body mass index; CCP, cyclic citrullinated peptide; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28, disease activity score 28; HAQ, health assessment questionnaire; DMARDs, disease-modifying anti-rheumatic drugs.

2. Variables associated with ALM index

Table 2 showed the association between ALM index and other variables. In unadjusted model, ALM index were significantly lower in female compared to that in male ($\beta = -1.575$, 95% confidence interval [CI], -2.246 to -0.903) and negatively associated with disease duration ($\beta = -0.069$, 95% CI, -0.133 to -0.006), DAS28 ($\beta = -0.387$, 95% CI, -0.729 to -0.045), and log-scaled HAQ score ($\beta = -0.691$, 95% CI, -1.222 to -0.159). Among BMD, T-score at total femur showed a positive correlation ($\beta = 0.349$, 95% CI, 0.047 to 0.651). In association between body mass and ALM index, the ALM index was positively correlated with the lean mass on arms and legs ($\beta = 0.837$, 95% CI, 0.621 to 1.052 and $\beta = 0.331$, 95% CI, 0.276 to 0.386, respectively), nega-

tively correlated with the fat fraction ($\beta = -0.034$, 95% CI, -0.064 to -0.005 and $\beta = -0.043$, 95% CI, -0.073 to -0.012, respectively).

In adjusted model with age, sex, and BMI, DAS28 and HAQ was significantly associated with ALM index ($\beta = -0.227$, 95% CI, -0.451 to -0.003 and $\beta = -0.510$, 95% CI, -0.826 to -0.193). There was not significantly association between ALM index and BMD. The ALM index on arms and legs showed significant association with the lean mass ($\beta = 0.738$, 95% CI, 0.202 to 1.275 and $\beta = 0.333$, 95% CI, 0.240 to 0.426, respectively) and the fat fraction ($\beta = -0.049$, 95% CI, -0.086 to -0.012 and $\beta = -0.051$, 95% CI, -0.096 to -0.007, respectively).

Table 3. Clinical characteristics of control group from the Korea National Health and Nutrition Examination Survey

Control group (n = 18,698)	
Age (yr)	46.0 (33.0 to 60.0)
Female	10,411 (55.7)
BMI (kg/m ²)	23.2 (20.9 to 25.5)
T-score	
Total spine	0.9 (0.8 to 1.0)
Femur neck	0.7 (0.7 to 0.8)
Total femur	0.8 (0.8 to 1.0)
Arms	
Fat mass (kg)	1.9 (1.4 to 2.4)
Lean mass (kg)	3.8 (3.1 to 5.4)
Fat fraction (%)	32.7 (22.4 to 41.6)
Legs	
Fat mass (kg)	5.3 (4.0 to 6.6)
Lean mass (kg)	12.7 (10.7 to 15.9)
Fat fraction (%)	29.9 (21.3 to 36.6)
ALM (kg/m ²)	6.5 (5.7 to 7.5)
Sarcopenia	5,045 (27.0)

The data is presented as median (interquartile range) or number (%). BMI, body mass index; ALM, appendicular lean mass.

3. Different tissue component between RA and control group

We used propensity score matching to obtain the control group from KNHANES data (Table 3). Table 4 showed comparison between control (n = 140) and RA group (n = 28). In model 1 matched with age and sex, RA group was significantly low BMI and low T-score at spine and femur. RA showed different tissue component from control group that low fat mass (1.7 ± 0.8 vs. 2.3 ± 0.7, P = 0.001) and low fat fraction (32.7 [24.5; 39.7] vs. 39.6 [31.6; 44.0], P = 0.004) in arms, but there was no significantly difference in fat mass in legs, lean mass in arms and legs, ALM index, and the proportion of patients with sarcopenia.

In model 2 matched with age, sex and BMI, we also observed that lower T-score of RA group compared to control group. There were no significant difference of fat and fat fraction between control and RA group. However, we observed that RA group had higher lean mass in legs and ALM index compared to control group (12.1 [11.0; 14.1] vs. 10.7 [9.7; 12.6], P = 0.004 and (6.3 [5.9; 7.1] vs. 5.8 [5.4; 6.3]), P = 0.016, respectively). There was no significant difference in the proportion of patients with sarcopenia.

Table 4. Propensity score matching between patients with rheumatoid arthritis and patients from the Korea National Health and Nutrition Examination Survey

	Model 1 ^{a)}			Model 2 ^{b)}		
	Control (n = 140)	RA (n = 28)	P-value	Control (n = 140)	RA (n = 28)	P-value
Age (yr)	59.0 (53.5 to 64.0)	58.5 (55.5 to 64.0)	0.710	62.0 (49.5 to 71.0)	58.5 (55.5 to 64.0)	0.273
Female	110 (78.6)	22 (78.6)	1.000	111 (79.3)	22 (78.6)	1.000
BMI (kg/m ²)	24.3 ± 3.0	21.8 ± 3.2	<0.001	22.0 (19.6 to 23.9)	21.5 (19.5 to 24.0)	0.758
T-score						
Total spine	0.9 (0.7 to 0.9)	-1.0 (-2.2 to 0.2)	<0.001	0.8 (0.7 to 1.0)	-1.0 (-2.2 to 0.2)	<0.001
Femur neck	0.7 (0.6 to 0.7)	-1.4 (-1.9 to -0.4)	<0.001	0.7 (0.6 to 0.7)	-1.4 (-1.9 to -0.4)	<0.001
Total femur	0.8 (0.8 to 0.9)	-1.2 (-1.9 to -0.4)	<0.001	0.8 (0.7 to 0.9)	-1.2 (-1.9 to -0.4)	<0.001
Arms						
Fat mass (kg)	2.3 ± 0.7	1.7 ± 0.8	0.001	1.9 ± 0.7	1.7 ± 0.8	0.333
Lean mass (kg)	3.6 (3.1 to 4.1)	3.5 (3.1 to 4.3)	0.907	3.3 (3.0 to 3.9)	3.5 (3.1 to 4.3)	0.177
Fat fraction ^{c)} (%)	39.6 (31.6 to 44.0)	32.7 (24.5 to 39.7)	0.004	36.3 (27.6 to 42.6)	32.7 (24.5 to 39.7)	0.120
Legs						
Fat mass (kg)	5.7 ± 1.8	5.7 ± 2.6	0.998	4.8 ± 1.7	5.7 ± 2.6	0.104
Lean mass (kg)	11.7 (10.5 to 13.3)	12.1 (11.0 to 14.1)	0.290	10.7 (9.7 to 12.6)	12.1 (11.0 to 14.1)	0.004
Fat fraction ^{c)} (%)	33.2 (26.4 to 37.7)	33.8 (25.5 to 37.9)	0.951	30.6 (25.2 to 35.7)	33.8 (25.5 to 37.9)	0.312
ALM (kg/m ²)	6.2 (5.7 to 6.9)	6.3 (5.9 to 7.1)	0.820	5.8 (5.4 to 6.3)	6.3 (5.9 to 7.1)	0.016
Sarcopenia (%)	25 (17.9)	6 (21.4)	0.859	51 (36.4)	6 (21.4)	0.190

The data is presented as mean ± standard deviation, median (interquartile range), or number (%).

^{a)}Matching with age and sex. ^{b)}Matching with age, sex, and BMI. ^{c)}The percentage of fat mass in total tissue mass. RA, rheumatoid arthritis; BMI, body mass index; ALM, appendicular lean mass.

DISCUSSION

We found that the higher the disease activity, the lower the ALM index in patients with RA. This may indicate that disability due to inflammatory cytokines or increased disease activity associated with RA may affect muscle mass. In addition, when compared to the general population with adjusting age and sex, patients with RA showed no difference in muscle mass but low fat. Taken together, pathophysiology of RA may affect the muscle and fat component of body.

Giels et al. [5] showed that rheumatoid factor positivity, increasing joint deformity, HAQ score, and CRP level was associated with abnormal body composition, but not DAS28 score. Munro and Capell [14] also showed that there was negative correlation between serum CRP level and muscle mass in women with RA. Our study also showed that RA disease activity and functional score were significantly associated with muscle mass in the association between ALM and DAS28 and HAQ.

In comparison between RA and control group, we did not find difference in ALM index in adjusted model with age and sex. Considering that DAS28 and HAQ are low values, ALM may not make much difference in the 2 groups. However, in adjusted model with age, sex, and BMI, we identified that the lean mass in legs and ALM index increased in RA group than in control group. As a result, it was confirmed that tissue component in patients with RA was significantly different from general population. Interestingly, Patients with RA seems to have lower fat mass in the arms and higher lean mass ratio in the legs than the general population. We suggested that fat mass ratio might be affected differently by arms and legs. Further research on RA and fat metabolism is needed.

It has been well known that Inflammatory cytokines are associated with muscle wasting in diseases, such as cancer, heart disease, and sepsis.[15] In addition, inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor were associated with reducing muscle mass.[16,17] In RA, Kramer et al. [18] suggested that higher tender joint count and serum IL-6 level was significantly associated with lower thigh muscle density using thigh computed tomography. In addition to the ALM index showing a deep association with disease activity in our study, it appears to show strong association between the pathophysiology of RA and muscle.

Our study had several limitations. First, this is cross-sectional study. In the longitudinal cohort, the measurement of ALM with RA and disease progression may provide a clearer relationship between disease activity and ALM. Second, we used KNHANES data as a control. Although similar patients were matched using propensity score, the timing and method of examination may differ. Third, we measured muscle mass but not muscle quality. By adding physical capacity or ability, we may add more information about the body component in patients with RA.

CONCLUSIONS

The appendicular muscle mass and disease activity were negatively correlated in patients with RA. In addition, appendicular tissue component may differ from the general population.

DECLARATIONS

Acknowledgments

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Ethics approval and consent to participate

This study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the Inje University Seoul Hospital Research Ethics Committee (IRB No. PAIK 2018-04-003).

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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