Muscle Wasting Aggravates Rheumatoid Arthritis in Elderly Patients as a Mediator

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Abstract

Background: Aging leads to loss of muscle mass causing functional limitation and reduced quality of life. Myopenia is a new universal term for the presence of clinically relevant muscle wasting. However, little is known about the prevalence of myopenia in elderly rheumatoid arthritis (RA) patients and its influence on RA pathogenesis and disease characteristics. We aimed to explore the characteristics of muscle mass and distribution and their clinical significance.

Methods: Consecutive RA patients were recruited and clinical data including disease activity (DAS28-CRP), physical function (health assessment questionnaire disability index, HAQ-DI) and radiographic indicators (modified Sharp score) were collected. The muscle mass and distribution were assessed by bioelectric impedance analysis. Myopenia was defined as appendicular skeletal muscle mass index (ASMI) ≤7.0kg/m2 (men) and ≤5.7kg/m2 (women).

Results: Among 643 RA patients recruited, there were 165 (25.7%) elderly patients (age≥60 years) with mean age 65.1±4.5 years. Compared with young patients (age<60 years), elderly RA patients had significantly higher DAS28-CRP (median 3.4 vs. 3.2), HAQ-DI (0.38 vs. 0.13) and modified total Sharp score (mTSS, 16 vs. 9), as well as higher proportion of myopenia (54.5% vs. 41.4%, all P<0.01). Elderly RA patients with myopenia (n=90, 14.0%) had significantly higher DAS28-CRP (3.6 vs. 3.0), HAQ-DI (0.50 vs. 0.12) and mTSS (21 vs. 7) than those in young RA patients without myopenia (n=280, 43.5%), and had higher mTSS (21 vs. 10) than those in elderly RA patients without myopenia (n=75, 11.7%, all P<0.0083). Multiple linear regression analysis after adjustment showed that both age (10 years as a unit, β=0.065~0.108) and ASMI (β= -0.369~ -0.220, all P<0.05) were correlated with DAS28-CRP, HAQ-DI and mTSS. Mediation analysis after adjustment showed that age had total and direct effects on DAS28-CRP, HAQ-DI or mTSS. ASMI partially mediated the associations between age and DAS28-CRP, HAQ-DI or mTSS (all P<0.05).

Conclusion: Our data firstly reveal that half of elderly RA patients manifest myopenia which aggravates the whole disease including disease activity, physical dysfunction and joint destruction as a mediator of age. Myopenia, a neglected complication in elderly RA should be emphasized.

Background

Rheumatoid arthritis (RA) is one of the most prevalent chronic inflammatory diseases leading to joint damage and disability [1]. The incidence of RA varies from 0.1–1.9% worldwide and increases with age [2, 3]. The cumulative lifetime risk of developing RA is less than 1% before 50 years old, but greatly increases at approximately 60 years old [4]. As life expectancy increases, there were more than 900 million elderly people (defined as ≥ 60 years old) in the world in 2015 [5]. In China, the number of elderly people was over 240 million in 2017 [6]. The estimated prevalence of RA in China is 0.42% and there were more than 5 million RA patients in 2013 [7]. According to a nationwide, multicenter, prospective Chinese Registry of Rheumatoid Arthritis (CREDIT), there were 32.7% elderly patients among the total

13210 patients in 2017, which predicts at least 1.6 million elderly RA patients in China now [8]. However, elderly RA patients are often excluded from clinical trials for their possible co-morbidities or other factors which might affect the results of intervention. Insufficient clinical data challenged the evidence-based management of elderly RA patients.

Aging is a multidimensional process comprising changes in different systems, such as altering innate immune system to become more active, but making the adaptive immune system declined [3]. These changes resulted in a special clinical manifestation of RA in elderly patients who are characterized by higher level of systemic inflammation and poor function [9]. Recent evidence showed that aging might also lead to loss of muscle mass which caused functional limitation and reduced quality of life in the elderly [10]. Myopenia is a new universal term for the presence of clinically relevant muscle wasting which might be caused by diseases such as muscular dystrophies, aging, persistent infection, chronic obstructive pulmonary disease, chronic kidney disease or cancers [11]. Benefit from the wide use of bioelectric impedance analysis (BIA) [12], the mass and distribution of muscle are available for the accurate assessment in daily clinical practice. Recently we reported 45.1% Chinese RA patients with myopenia who manifested high disease activity as well as severe joint destruction [13]. However, the prevalence of myopenia in elderly RA patients and its influence on RA pathogenesis and disease characteristics have not yet been elucidated. Here, we further investigated the characteristics of muscle mass and distribution in elderly RA patients, aiming to explore their impact on RA disease characteristics.

Methods

Patients and groups

Consecutive Chinese patients with RA who fulfilled the 1987 revised criteria of the American College of Rheumatology (ACR) [14] or the 2010 ACR/European League Against Rheumatism (EULAR) criteria for the classification of RA [15] were recruited at Department of Rheumatology, Sun Yat-Sen Memorial Hospital, Guangzhou, P.R China from August 2015 to June 2019. Exclusion criteria included the following: pregnancy, severe mental disorders, implanted electronic devices, patients with other autoimmune diseases (e.g. systemic lupus erythematosus, systemic sclerosis, dermatomyositis, etc), severe infection, organ dysfunction including liver, renal and respiratory dysfunction, malignancy, or unable to stand stably and independently (e.g. stroke, severe spinal deformity, etc). This study was approved by the Ethics Committee of Sun Yat-Sen Memorial Hospital (SYSEC-2009-06 and SYSEC-KY-KS-012). All patients signed informed consent.

All RA patients were classified into young (age < 60 years) and elderly RA groups (age ≥ 60 years), young onset (onset age < 60 years) and elderly onset RA groups (onset age ≥ 60 years) according to age and onset age respectively.

Clinical Assessment

Demographic and clinical data were collected at enrollment, including age, gender, disease duration, onset age, body mass index (BMI), smoking habits, previous medications including the usage of glucocorticoids, conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) and biologic DMARDs (bDMARDs), comorbidities including hypertension, diabetes, dyslipidemia and fatty liver, disease activity and physical function (health assessment questionnaire disability index, HAQ-DI) indicators as we described previously [13]. Disease duration was divided into 3 categories: ≤6 months (short), 6–24 months (intermediate), and ≥24 months (long). Disease activity was assessed with Disease Activity Score in 28 joints with four variables including C reactive protein (DAS28-CRP) or erythrocyte sedimentation rate (DAS28-ESR), Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI). Disease activity defined by DAS28-CRP was divided into four categories: high disease activity (HDA, DAS28-CRP > 5.1), moderate disease activity (MDA, 3.2 ≤ DAS28-CRP ≤ 5.1), low disease activity (LDA, 2.6 ≤ DAS28-CRP < 3.2), and remission (DAS28-CRP < 2.6).

Radiographic Assessment

Conventional radiographs of bilateral hands and wrists (anteroposterior view) of all patients were performed at enrollment and assessed according to Sharp/van der Heijde-modified Sharp score including modified total Sharp score (mTSS), joint erosion (JE) and joint space narrowing (JSN) subscores as we described previously [16]. The mean intra-class correlation coefficient (ICC) for reliability and inter-observer agreement was 0.953.

Muscle Assessment

The mass and distribution of muscle in trunk and appendicular extremities were assessed by BIA using an InBody 230 device (Biospace Co., Shanghai, China) as we described previously [13]. Appendicular skeletal muscle mass index (ASMI) was defined by appendicular skeletal muscle mass/height^2 (kg/m^2). Myopenia was defined by ASMI ≤ 7.0 kg/m^2 in men and ≤ 5.7 kg/m^2 in women according to Asian Working Group for Sarcopenia (AWGS) [17].

Statistical analysis

IBM SPSS Statistics software for Windows version 25.0 (IBM, Armonk, NY, USA) was used for statistical analyses. According to distributions, values of continuous variables were presented as mean and standard deviation (SD) or median with inter-quartile range (IQR). Two independent samples t-Test or the Mann-Whitney test was used for comparison between two independent groups. Analysis of Variance (ANOVA) or Kruskal-Wallis analysis of variance on ranks were used among four groups according to distributions. Categorical variables were presented as numbers and percentages. Chi-square test or Fisher's exact test was used to compare categorical variables. Bonferroni correction was used for multiple comparisons in subgroups. Correlations of age, ASMI and clinical indicators were analyzed by

Spearman's rank order correlation test. All significance tests were two-tailed and were conducted at the 5% significance level.

Univariate and multiple linear regression analysis was used to identify the association between age (10 years as a unit) and ASMI (independent variables) with RA disease characteristics (dependent variables) including disease activity (DAS28-CRP), physical function (HAQ-DI) and joint destruction (mTSS), and adjusted for the confounders including gender, disease duration, active smoking, BMI, rheumatoid factor (RF) status, anti-cyclic citrullinated peptide antibody (ACPA) status, previous medications (categorized by treatment naïve, glucocorticoids, csDMARDs and bDMARDs therapy due to the number of cases), comorbidities (including hypertension, diabetes, dyslipidemia, fatty liver and heart disease) with or without DAS28-CRP. In fitting these multifactorial models, HAQ-DI was normalized by a natural square root transformation while mTSS was normalized by a $\lg(X + 1)$ transformation to make sure the models.

Mediation analysis is widely used to quantify how an exposure or intervention affects outcome [18]. It was performed to identify the effect of ASMI (mediator) on the association between age (10 years as a unit, independent variable) and RA disease characteristics (dependent variables) including disease activity (DAS28-CRP), physical function HAQ-DI and joint destruction (mTSS). Confounders mentioned above were adjusted in two models due to the number of factors. Mediation analysis was conducted on SPSS utilizing PROCESS macro (Version 3.3) provided by Andrew F. Hayes [19]. The bootstrap method was used as it was free from assumptions regarding the shape of the sampling distribution of the indirect effect and had better control on type I errors [20]. The number of bootstrap samples was 10,000. Bootstrap bias-corrected 95% confidence intervals (CI) was calculated and when they didn't contain zero, they were considered significant.

Results

Demographic characteristics of all RA patients

There were 643 RA patients recruited with 82.3% female, mean age 49.7 ± 12.9 years and median disease duration 48 (IQR 21,108) months. There were 31 (4.8%) early RA patients (short disease duration) and 439 (68.3%) with long disease duration. There were 100 (15.6%) RA patients in HDA, 224(34.8%) in MDA, 90 (14.0%) in LDA, and 229 (35.6%) in remission. There were 114 (17.7%) RA patients without previous glucocorticoids or DMARDs therapy for at least 6 months before enrolment (treatment naïve, Table 1). There were 94 (14.6%) patients with hypertension, 52 (8.1%) patients with diabetes, 55 (8.6%) patients with dyslipidemia, 52 (8.1%) patients with fatty liver and 28 (4.4%) patients with heart disease.

Table 1

Clinical characteristics of RA patients in age subgroups

Characteristics	All patients (n = 643)	Young RA patients (n = 478)	Elderly RA patients (n = 165)	P*
Age, years, mean ± SD	49.7 ± 12.9	44.4 ± 10.3	65.1 ± 4.5	< 0.001
Onset age, years, mean ± SD	43.6 ± 13.0	39.1 ± 10.7	56.7 ± 9.9	< 0.001
Female, n (%)	529 (82.3)	410 (85.8)	119 (72.1)	< 0.001
Disease duration, months, median (IQR)	48 (21,108)	48 (19,96)	72 (23,138)	0.004
Active smoking, n (%)	95 (14.8)	55 (11.5)	40 (24.2)	< 0.001
BMI, kg/m^2, mean ± SD	21.9 ± 3.3	21.8 ± 3.3	22.2 ± 3.4	0.194
ASMI, kg/m^2, mean ± SD	6.0 ± 0.9	6.0 ± 0.9	5.9 ± 1.1	0.212
Appendicular skeletal muscle mass, kg, mean ± SD	15.0 ± 3.4	15.2 ± 3.2	14.7 ± 3.9	0.169
Trunk muscle mass, kg, mean ± SD	16.8 ± 3.3	16.8 ± 3.1	16.7 ± 3.6	0.811
Myopenia, n (%)	288 (44.8)	198 (41.4)	90 (54.5)	0.003
Core disease activity indicators				
28TJC, median (IQR)	2 (0,6)	2 (0,5)	2 (0,9)	0.087
28SJC, median (IQR)	1 (0,4)	1 (0,4)	1 (0,5)	0.373
PtGA, cm, median (IQR)	3 (1,5)	3 (1,5)	4 (2,6)	0.013
PrGA, cm, median (IQR)	3 (1,5)	3 (1,5)	4 (2,6)	0.008
Pain VAS, cm, median (IQR)	2 (2,4)	2 (2,4)	3 (2,4)	0.120
ESR, mm/h, median (IQR)	28 (15,51)	26 (14,44)	41 (22,68)	< 0.001

*Compared between young and elderly RA patients by two independent samples t-Test, Mann-Whitney test or Chi-square test. Significant differences are shown in bold.

28TJC, 28-joint tender joint counts; 28SJC, 28-joint swollen joint counts; PtGA, patient global assessment of disease activity; PrGA, provider global assessment of disease activity; Pain VAS, pain visual analogue scale; RF, rheumatoid factor; ACPA, Anti-cyclic citrullinated peptide antibody; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; bDMARDs, biological disease-modifying antirheumatic drugs.

Characteristics	All patients (n = 643)	Young RA patients (n = 478)	Elderly RA patients (n = 165)	P*
CRP, mg/L, median (IQR)	4.24 (3.28,16.70)	3.54 (3.28,14.50)	5.41 (3.28,19.40)	0.041
DAS28-CRP, median (IQR)	3.2 (2.0,4.5)	3.2 (2.0,4.3)	3.4 (2.3,5.0)	0.026
DAS28-ESR, median (IQR)	3.9 (2.7,5.1)	3.7 (2.6,5.0)	4.0 (3.0,5.7)	0.001
SDAI, median (IQR)	11.3 (4.3,22.1)	10.5 (4.3,20.6)	13.3 (5.2,29.3)	0.016
CDAI, median (IQR)	10.0 (4.0,20.0)	10.0 (3.0,18.3)	12.0 (4.0,25.5)	0.025
Positive RF, n (%)	422 (65.6)	308 (64.4)	114 (69.1)	0.278
Positive ACPA, n (%)	451 (70.1)	343 (71.8)	108 (65.5)	0.127
HAQ-DI, median (IQR)	0.25 (0.00,0.75)	0.13 (0.00,0.63)	0.38 (0.00,1.00)	< 0.001
Radiographic indicators				
mTSS, median (IQR)	11 (4,31)	9 (3,29)	16 (6,42)	< 0.001
JSN subscore, median (IQR)	3 (0,12)	2 (0,11)	4 (1,18)	0.039
JE subscore, median (IQR)	8 (3,20)	6 (2,17)	11 (4,26)	< 0.001
Previous medications				
Treatment naïve, n (%)	114 (17.7)	85 (17.8)	29 (17.6)	0.952
Glucocorticoids, n (%)	348 (54.1)	252 (52.7)	96 (58.2)	0.225
csDMARDs, n (%)	491 (76.4)	371 (77.6)	120 (72.7)	0.203
bDMARDs, n (%)	38 (5.9)	28 (5.9)	10 (6.1)	0.924

*Compared between young and elderly RA patients by two independent samples t-Test, Mann-Whitney test or Chi-square test. Significant differences are shown in bold.

28TJC, 28-joint tender joint counts; 28SJC, 28-joint swollen joint counts; PtGA, patient global assessment of disease activity; PrGA, provider global assessment of disease activity; Pain VAS, pain visual analogue scale; RF, rheumatoid factor; ACPA, Anti-cyclic citrullinated peptide antibody; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; bDMARDs, biological disease-modifying antirheumatic drugs.

Clinical Characteristics Of Elderly Ra Patients

There were 165 (25.7%) elderly RA patients with mean age 65.1 ± 4.5 years. There were two peaks of age distribution in 50 ~ 55 years and 60 ~ 65 years among all RA patients (Fig. 1A). The mean onset age of all RA patients was 43.6 ± 13.0 years with a peak about 40 ~ 55 years (Fig. 1B). Compared with young patients, elderly RA patients had significantly higher proportion of male (27.9% vs. 14.2%), higher core disease activity indicators including PtGA, PrGA, ESR and CRP, higher disease activity scores including DAS28-CRP (median 3.4 vs. 3.2), DAS28-ESR (median 4.0 vs. 3.7), SDAI (median 13.3 vs. 10.5) and CDAI (median 12.0 vs. 10.0), higher HAQ-DI (median 0.38 vs. 0.13) and higher mTSS (median 16 vs. 9), as well as older onset age (56.7 ± 9.9 years vs. 39.1 ± 10.7 years) and longer disease duration (median 72 months vs. 48 months, all $P < 0.05$, Table 1). The elderly RA patients also had higher rates of hypertension (33.3% vs. 8.2%) and diabetes (17.0% vs. 5.0%, both P□0.05).

Among 165 elderly RA patients, there were 70 (42.4%) patients with elderly onset. Compared with elderly patients with young onset, elderly onset RA patients had higher proportion of male (38.6% vs. 20.0%), higher proportion of active smoking (35.7% vs. 15.8%), but lower mTSS (median 8 vs. 23) as well as shorter disease duration (median 20 months vs. 120 months, all $P < 0.05$, data not shown).

Muscle Characteristics Of Elderly Ra Patients

The mean ASMI of female RA patients was 5.73 ± 0.77 kg/m^2 and 7.07 ± 0.92 kg/m^2 in male patients. There were 288 (44.8%) RA patients with myopenia including 242 (45.7%) in female patients and 46 (40.4%) in male patients. Compared with young patients, elderly RA patients had higher proportion of myopenia (54.5% vs. 41.4%, $P = 0.003$, Table 1). There were no significant differences in muscle mass and distribution, prevalence of myopenia between elderly RA patients with young onset and elderly onset.

Clinical Characteristics Of Elderly Ra Patients With Myopenia

Compared with those without myopenia, RA patients with myopenia had significantly longer disease duration (median 72 months vs. 45 months), higher core disease activity indicators including 28TJC, 28SJC, PtGA, PrGA, Pain VAS, ESR, CRP and higher proportion of positive RF, higher disease activity scores including DAS28-CRP (median 3.5 vs. 3.0), DAS28-ESR (median 4.0 vs. 3.6), SDAI (median 13.1 vs. 10.3) and CDAI (median 12.0 vs. 9.0), higher HAQ-DI (median 0.38 vs. 0.13) as well as higher radiographic scores including mTSS (median 18 vs. 7), JSN subscore (median 6 vs. 1) and JE subscore (median 12 vs. 6, all $P < 0.05$, Table 2).

Table 2

Clinical characteristics of RA patients in myopenia subgroups

Characteristics	Non-myopenia (n = 355)	Myopenia (n = 288)	P*
Age, years, mean ± SD	49.7 ± 11.4	49.8 ± 14.4	0.917
Onset age, years, mean ± SD	44.4 ± 11.5	42.7 ± 14.6	0.101
Female, n (%)	287 (80.8)	242 (84.0)	0.293
Disease duration, months, median (IQR)	45 (17,90)	72 (24,120)	< 0.001
Active smoking, n (%)	53 (14.9)	42 (14.6)	0.902
BMI, kg/m^2, mean ± SD	23.4 ± 3.0	20.0 ± 2.6	< 0.001
Core disease activity indicators			
28TJC, median (IQR)	2 (0,5)	2 (0,7)	0.011
28SJC, median (IQR)	1 (0,4)	2 (0,5)	0.010
PtGA,cm, median (IQR)	2 (0,5)	4 (1,6)	0.003
PrGA, cm, median (IQR)	2 (1,5)	4 (1,6)	0.002
Pain VAS,cm, median (IQR)	2 (1,4)	3 (2,4)	0.005
ESR, mm/h, median (IQR)	26 (15,43)	32 (16,68)	0.002
CRP, mg/L, median (IQR)	3.45 (3.28,11.10)	6.26 (3.28,24.15)	0.001
DAS28-CRP, median (IQR)	3.0 (1.9,4.2)	3.5 (2.3,5.0)	0.001
DAS28-ESR, median (IQR)	3.6 (2.5,4.9)	4.0 (2.9,5.7)	0.002
SDAI, median (IQR)	10.3 (3.3,19.3)	13.1 (5.1,25.9)	0.002
CDAI, median (IQR)	9.0 (3.0,18.0)	12.0 (4.0,24.0)	0.004
Positive RF, n (%)	221 (62.3)	201 (69.8)	0.045
Positive ACPA, n (%)	248 (69.9)	203 (70.5)	0.863
HAQ-DI, median (IQR)	0.13 (0.00,0.50)	0.38 (0.00,1.00)	< 0.001

*Compared with RA patients without myopenia by two independent samples t-Test, Mann-Whitney test or Chi-square test.

Significant differences are shown in bold.

28TJC, 28-joint tender joint counts, 28SJC, 28-joint swollen joint counts; PtGA, patient global assessment of disease activity; PrGA, provider global assessment of disease activity; Pain VAS, pain visual analogue scale; RF, rheumatoid factor; ACPA, Anti-cyclic citrullinated peptide antibody.

Characteristics	Non-myopenia (n = 355)	Myopenia (n = 288)	P*
Radiographic assessment			
mTSS, median (IQR)	7 (3,21)	18 (6,51)	< 0.001
JSN subscore, median (IQR)	1 (0,6)	6 (1,23)	< 0.001
JE subscore, median (IQR)	6 (2,13)	12 (4,29)	< 0.001
*Compared with RA patients without myopenia by two independent samples t-Test, Mann-Whitney test or Chi-square test.			
Significant differences are shown in bold.			
28TJC, 28-joint tender joint counts, 28SJC, 28-joint swollen joint counts; PtGA, patient global assessment of disease activity; PrGA, provider global assessment of disease activity; Pain VAS, pain visual analogue scale; RF, rheumatoid factor; ACPA, Anti-cyclic citrullinated peptide antibody.			

According to age and ASMI, all RA patients were divided into four subgroups. There were 280 (43.5%) young RA patients without myopenia, 198 (30.8%) young RA patients with myopenia, 75 (11.7%) elderly RA patients without myopenia and 90 (14.0%) elderly RA patients with myopenia. Among four subgroups, there were significant differences in disease activity (DAS28-CRP varied from median 3.0 to 3.6), functional (HAQ-DI varied from 0.12 to 0.50) and radiographic indicators (mTSS varied from 7 to 21, all $P < 0.05$). Further multiple comparisons showed that elderly RA patients with myopenia had significantly higher core disease activity indicators including PtGA, PrGA, Pain VAS, ESR, CRP, higher disease activity scores including DAS28-CRP, DAS28-ESR, SDAI and CDAI, higher HAQ-DI and radiographic indicators including mTSS, JSN and JE subscores than those in young RA patients without myopenia (all $P < 0.0083$, Table 3).

Table 3

Clinical characteristics of RA patients in age and myopenia subgroups

Characteristics	Young RA patients		Elderly RA patients		P#
	Non-myopenia (n = 280)	Myopenia (n = 198)	Non-myopenia (n = 75)	Myopenia (n = 90)	
Age, years, mean ± SD	45.6 ± 9.0	42.8 ± 11.7*	65.1 ± 4.4*§	65.1 ± 4.6*§	< 0.001
Onset age, years, mean ± SD	41.0 ± 9.4	36.5 ± 11.8*	57.2 ± 9.2*§	56.3 ± 10.5*§	< 0.001
Female, n (%)	234 (83.6)	176 (88.9)	53 (70.7)§	66 (73.3)§	< 0.001
Disease duration, months, median (IQR)	40 (17,84)	69 (24,108)*	72 (14,144)*	78 (24,135)*	0.016
Active smoking, n (%)	35 (12.5)	20 (10.1)	18 (24.0)§	22 (24.4)*§	0.001
BMI, kg/m^2, mean ± SD	23.2 ± 3.1	19.8 ± 2.5*	24.2 ± 2.9*§	20.5 ± 2.7*†	< 0.001
Core disease activity indicators					
28TJC, median (IQR)	2 (0,5)	2 (1,7)	2 (0,6)	4 (0,10)	0.048
28SJC, median (IQR)	1 (0,4)	1 (0,4)	1 (0,4)	2 (0,6)	0.106
PtGA, cm, median (IQR)	2 (0,5)	3 (1,6)	3 (2,5)	4 (2,6)*	0.006
PrGA, cm, median (IQR)	2 (0,5)	3 (1,5)	3 (2,5)	4 (2,6)*	0.005
Pain VAS, cm, median (IQR)	2 (1,4)	3 (2,4)	2 (2,4)	3 (2,6)*	0.040

#Comparison in four groups by ANOVA, Chi-square test or Kruskal-Wallis test. P < 0.05.

* Compared with young RA patients without myopenia in Bonferroni correction, P < 0.0083.

§ Compared with young RA patients with myopenia in Bonferroni correction, P < 0.0083.

† Compared with elderly RA patients without myopenia in Bonferroni correction, P < 0.0083. Significant differences are shown in bold.

28TJC, 28-joint tender joint counts, 28SJC, 28-joint swollen joint counts; PtGA, patient global assessment of disease activity; PrGA, provider global assessment of disease activity; Pain VAS, pain visual analogue scale; RF, rheumatoid factor; ACPA, Anti-cyclic citrullinated peptide antibody.

Characteristics	Young RA patients		Elderly RA patients		P#
	Non-myopenia (n = 280)	Myopenia (n = 198)	Non-myopenia (n = 75)	Myopenia (n = 90)	
ESR, mm/h, median (IQR)	25 (14,39)	27 (14,54)	38 (20,62)*	45 (22,75)*§	< 0.001
CRP, mg/L, median (IQR)	3.30 (3.28,11.08)	5.56 (3.28,23.85)	4.69 (3.28,11.20)	7.77 (3.28,24.68)*	0.006
DAS28-CRP, median (IQR)	3.0 (1.9,4.1)	3.4 (2.2,4.7)*	3.1 (2.2,4.5)	3.6 (2.3,5.4)*	0.002
DAS28-ESR, median (IQR)	3.5 (2.5,4.9)	3.9 (2.8,5.4)	3.9 (2.9,5.1)	4.4 (3.0,6.3)*	0.002
SDAI, median (IQR)	9.2 (3.1,18.9)	11.9 (4.8,23.5)	11.0 (4.6,22.2)	15.3 (5.7,33.5)*	0.012
CDAI, median (IQR)	8.0 (2.0,18.0)	11.0 (4.0,20.0)	10.0 (4.0,20.0)	13.5 (4.0,30.0)*	0.017
Positive RF, n (%)	176 (62.9)	132 (66.7)	45 (60.0)	69 (76.7)	0.073
Positive ACPA, n (%)	201 (71.8)	142 (71.7)	47 (62.7)	61 (67.8)	0.417
HAQ-DI, median (IQR)	0.12 (0.00,0.50)	0.25 (0.00,0.88)*	0.25 (0.00,0.75)	0.50 (0.12,1.28)*	< 0.001
Radiographic indicators					
mTSS, median (IQR)	7 (2,17)	17 (5,49)*	10 (4,31)*	21 (9,53)*	< 0.001
JSN subscore, median (IQR)	1 (0,6)	6 (1,23)*	2 (0,6) §	6 (1,27)*†	< 0.001
JE subscore, median (IQR)	5 (1,11)	11 (3,29)*	9 (3,24) *	13 (6,32)*	< 0.001
#Comparison in four groups by ANOVA, Chi-square test or Kruskal-Wallis test. P < 0.05.					
* Compared with young RA patients without myopenia in Bonferroni correction, P < 0.0083.					
§ Compared with young RA patients with myopenia in Bonferroni correction, P < 0.0083.					
† Compared with elderly RA patients without myopenia in Bonferroni correction, P < 0.0083. Significant differences are shown in bold.					
28TJC, 28-joint tender joint counts, 28SJC, 28-joint swollen joint counts; PtGA, patient global assessment of disease activity; PrGA, provider global assessment of disease activity; Pain VAS, pain visual analogue scale; RF, rheumatoid factor; ACPA, Anti-cyclic citrullinated peptide antibody.					

Linear regression analysis of age and ASMI associated with RA disease characteristics

Spearman's rank order correlation test showed that age was positively correlated with DAS28-CRP (r = 0.127), HAQ-DI (r = 0.225) and mTSS (r = 0.203, all P < 0.001), while ASMI was negatively correlated with DAS28-CRP (r= -0.131), HAQ-DI (r= -0.195) and mTSS (r= -0.305, all P < 0.001). Linear regression analysis was used to identify the association of age and ASMI with RA disease characteristics. Univariate linear regression analysis showed that age was positively correlated with DAS28-CRP (β = 0.157), HAQ-DI (β = 0.082) and mTSS (β = 0.090), while ASMI was negatively correlated with DAS28-CRP (β= -0.244), HAQ-DI (β= -0.117) and mTSS (β= -0.197, all P < 0.01).

Adjusted for confounding factors including gender, disease duration, BMI, active smoking, RF status, ACPA status, previous medications and comorbidities, multiple linear regression analysis showed that age was still positively correlated with DAS28-CRP (β = 0.108), HAQ-DI (β = 0.065) and mTSS (β = 0.085), while ASMI was negatively correlated with DAS28-CRP (β= -0.369), HAQ-DI (β= -0.220) and mTSS (β= -0.284, all P < 0.05). Disease activity can affect physical dysfunction and joint destruction in RA, so additional DAS28-CRP was further adjusted as a confounding factor and the results showed that age was still positively correlated with HAQ-DI (β = 0.041) and mTSS (β = 0.077), while ASMI was negatively correlated with HAQ-DI (β= -0.139) and mTSS (β= -0.261, all P < 0.001, Table 4).

Mediation analysis of ASMI on the association between age and RA disease characteristics

Mediation analysis was performed to identify the effect of ASMI on the association between age and DAS28-CRP. Adjusted for confounding factors including gender, disease duration, BMI, active smoking, RF status, ACPA status, previous medications, age had total effect and direct effect on DAS28-CRP (β = 0.128, P = 0.002 and β = 0.089, P = 0.031). The path from age to DAS28-CRP through mediation of ASMI was statistically significant (P□0.05). Further adjusted for additional DAS28-CRP, age also had total effects and direct effects on HAQ-DI (β = 0.046, P□0.001 and β = 0.034, P = 0.002) and mTSS (β = 0.076, P□0.001 and β = 0.052, P = 0.004), while the path from age to HAQ-DI or mTSS through mediation of ASMI were statistically significant (both P□0.05). These results indicated that ASMI partially mediated the association between age and DAS28-CRP, HAQ-DI or mTSS, which were further confirmed by mediation analysis after adjustment of comorbidities instead of previous medication (Fig. 2).

Discussion

This is the first report about the characteristics of muscle mass and distribution in a large-scale study of elderly RA patients and their impact on RA disease characteristics.Half of elderly Chinese RA patients (54.5%) manifested myopenia who had the most severe disease of RA as higher disease activity with more than 4 folds of physical dysfunction (HAQ-DI) and 3 folds of joint destruction (mTSS), indicating a new phenotype of RA. Myopenia might aggravate the whole disease of RA as a mediator of age, which

imply that myopenia should be emphasized as an important complication in RA especially in elderly patients.

Remarkable changes of immune systems with aging result in immunosenescence. During this process, aging activates innate immune system resulting in increased systemic inflammatory indicators including ESR and CRP, as well as inflammatory cytokines such as TNF-α and IL-6 [3]. A new term named inflamm-aging was developed in 2000 for the condition that high levels of proinflammatory markers express in cells and tissues of older organisms [21]. Local and systemic inflammation not only cause impaired anabolism and increased protein breakdown of myofiber, but also play a critical role on the onset of muscle wasting [22]. In clinical studies, muscle wasting was found in 20% Italian RA patients and 49% Japanese RA patients [23, 24]. In our previous study, there were 45.1% Chinese RA patients with myopenia which was more than 3 folds higher than that in controls of white-collar employees [13]. Longitudinal study showed that inhibition of IL-6 by tocilizumab, an IL-6 receptor blocker, increased muscle mass in RA patients [25]. In our present study, elderly RA patients had higher disease activity indicators as well as higher proportion of myopenia compared with young patients, which confirmed the impacts of inflammation on muscle wasting in RA patients. On the other hand, a brand-new finding showed that IL-17 and/or TNFα leaded to dysfunction of human myoblasts and increased their secretion of IL-6, indicating muscle cell dysfunction could promote inflammation [26]. We revealed that ASMI partially mediated the association between age and DAS28-CRP, which might be a clinical evidence that inflamm-aging affects not only joints, but also muscle which in turn aggravates inflammation in RA.

Structural and electrophysiological changes in skeletal muscle are frequently found in humans over 60 years of age and followed by a progressive age-related decline [10]. Human manifests decline in muscle mass and strength of about 1% per year from the age of around 40 years [27]. Low muscle mass combined with low muscle strength and physical performance in the elderly people were academically recognized as a new independent disease called sarcopenia, which highlighted the relationship of age-associated muscle wasting and physical limitation in the elderly people [28–30]. Muscle wasting is also associated with joint dysfunction in RA patients. Clinical study from Jon T. Giles et al showed that the mean HAQ score was 0.81 units lower in RA patients with the highest quartile of appendicular lean mass than those with the lowest quartile [31], while Hanh-Hung Dao et al found similar results that HAQ score was negatively correlated with appendicular lean mass in RA patients [32]. In our study, negative correlations of age and ASMI as well as ASMI and HAQ-DI were both significant after adjusted for confounding factors including disease activity (DAS28-CRP). Further mediation analysis showed ASMI partially mediated the association between age and HAQ-DI, which supported the impact of age-associated muscle wasting on physical dysfunction in elderly RA patients.

Numerous evidences showed that older RA patients had more severe joint destruction [33–35]. Recent study including five longitudinal cohorts showed that increased age was associated with more severe joint destruction in RA patients [36]. Aging disturbs the homoeostasis of skeletal muscle and the cross-talk between skeletal muscle and bone has become a research hotspot in the field of aging these years [37, 38]. Skeletal muscle functions in an endocrine manner by secreting various myokines such as irisin,

myostatin, osteocalcin and so on, which are involved in osteoclastogenesis [39]. Irisin, a myokine produced from skeletal muscle after exercise, can increase osteoblast differentiation and suppresses osteoclast differentiation [40], while myostatin, as a negative regulator of muscle growth and regeneration, can enhance bone degradation by RANKL-induced osteoclastogenesis [41]. To find out how aging influence the cross-talk between skeletal muscle and bone from a clinical perspective, we found that half of elderly RA patients (54.5%) manifested myopenia who had the worst joint destruction than others. After adjusted for confounding factors especially disease duration and disease activity (DAS28-CRP), mediation analysis revealed that ASMI partially mediated the association between age and mTSS, which suggested that myopenia might aggregate joint destruction through the cross-talk of muscle and bone as a result of aging in RA patients.

RA patients have high prevalence of comorbidities, such as hypertension, diabetes and cardiovascular disease, which increase the mortality and lead to worse outcome [8, 42–45]. Muscle wasting is associated with poor health outcomes including functional decline, falls and mortality in varies diseases such as cardiovascular diseases, respiratory diseases and cancers, which is considered as a comorbidity in those diseases especially in elderly people [46]. However, systemic inflammation in RA can affect various organs and tissues including muscle and cause inflammatory myopathy or muscle atrophy [47]. As a result, muscle wasting is more likely to be the consequence of RA, implying that myopenia might be an underscored complication rather than comorbidity in RA. In our study, more than half of elderly RA patients (54.5%) manifest myopenia which aggravates disease activity, physical dysfunction and joint destruction. Thus, myopenia, as a common but neglected complication in elderly RA patients should be concerned in future clinical practice.

There were several limitations in our study. First, categorical definition of elderly people varies from 60 years or 65 years of age especially in western countries [48]. We defined elderly patients as age ≥ 60 years in this paper according to the latest version of Chinese law for elderly people protection in 2018. There were only 76 (11.8%) RA patients with age ≥ 65 years and 70 (10.9%) elderly onset RA patients in this paper which limited further analysis. Second, most of the recruited patients were diagnosed with established RA and 68.3% of them had long disease duration which might be a significant confounding factor affecting joint destruction. Although the mediating effects of ASMI between age and DAS28-CRP, HAQ-DI or mTSS are significant after adjustment of disease duration, early RA patients are needed to confirm these results directly. Third, there were only 114 (17.7%) RA patients with treatment naïve and only previous therapeutic categories, but not each specific drug was adjusted in this real-world study. A prospective cohort study on large scale of treatment naïve patients with early RA especially elderly and elderly-onset RA is necessary in future to verify the influences of aging on muscle and clinical outcomes in RA.

Conclusions

In conclusion, half of elderly RA patients manifest myopenia which aggravates the whole disease including disease activity, physical dysfunction and joint destruction as a mediator of age. Myopenia, a

neglected complication in RA especially in elderly patients should be emphasized.

Abbreviations

RA:rheumatoid arthritis; BIA:bioelectric impedance analysis; EULAR:European League Against Rheumatism; ACR:American College of Rheumatology; BMI:body mass index; csDMARDs:conventional synthetic disease modifying anti-rheumatic drugs; bDMARDs:biologic disease modifying anti-rheumatic drugs; HAQ-DI:health assessment questionnaire disability index; DAS28-CRP:Disease Activity Score in 28 joints with four variables including C reactive protein; DAS28-ESR:Disease Activity Score in 28 joints with four variables including erythrocyte sedimentation rate; CRP:C reactive protein; ESR:erythrocyte sedimentation rate; SDAI:Simplified Disease Activity Index; CDAI:Clinical Disease Activity Index; HDA:high disease activity; MDA:moderate disease activity; LDA:low disease activity; mTSS:modified total Sharp score; JE:joint erosion; JSN:joint space narrowing; ICC:intra-class correlation coefficient; ASMI:appendicular skeletal muscle mass index; AWGS:Asian Working Group for Sarcopenia; SD:standard deviation; IQR:inter-quartile range; ANOVA:Analysis of Variance; CI:confidence intervals; 28TJC:28-joint tender joint counts; 28SJC:28-joint swollen joint counts; PtGA:patient global assessment of disease activity; PrGA:provider global assessment of disease activity; Pain VAS:pain visual analogue scale; RF:rheumatoid factor; ACPA:Anti-cyclic citrullinated peptide antibody.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Sun Yat-Sen Memorial Hospital (SYSEC-2009-06 and SYSEC-KY-KS-012). All patients signed informed consent.

Consent for publication

All participants have approved to publish the data in this manuscript.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests to disclose.

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Author contributions

All authors contributed to the final manuscript. Jian-Da Ma and Chu-Tao Chen contributed equally to this work, including conceiving and designing the study, reading and analyzing documents, performing the statistical analysis, and drafting the manuscript. Corresponding authors Dong-Hui Zheng and Lie Dai also conceived and participated in its design, advised on the search, read and analyzed documents, and edited the paper. Jian-Zi Lin, Qian-Hua Li and Yan-Hui Xu participated in clinical assessment and muscle measurement of RA patients and critically revised the manuscript. Le-Feng Chen and Ze-Hong Yang participated in the radiographic assessment and critically revised the manuscript. All authors read and approved the final manuscript.

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Figures

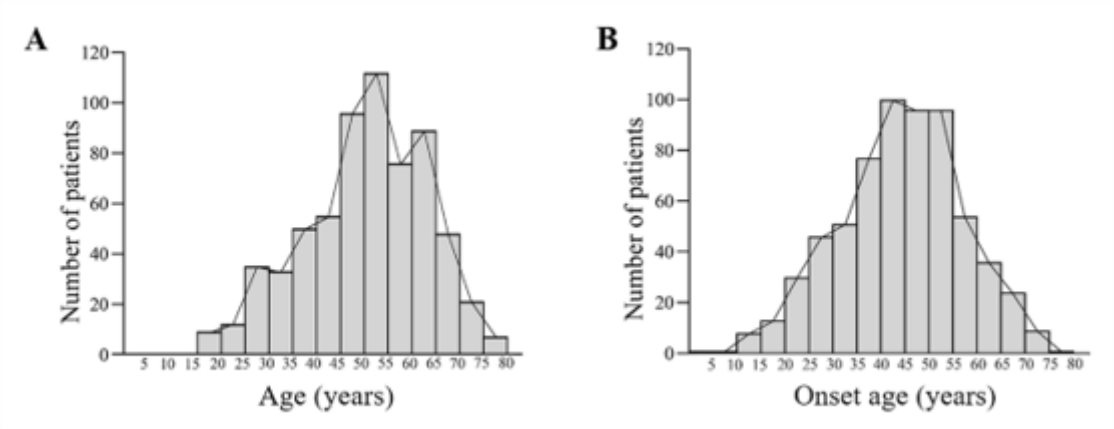

Figure 1

Distribution of age and onset age among RA patients.

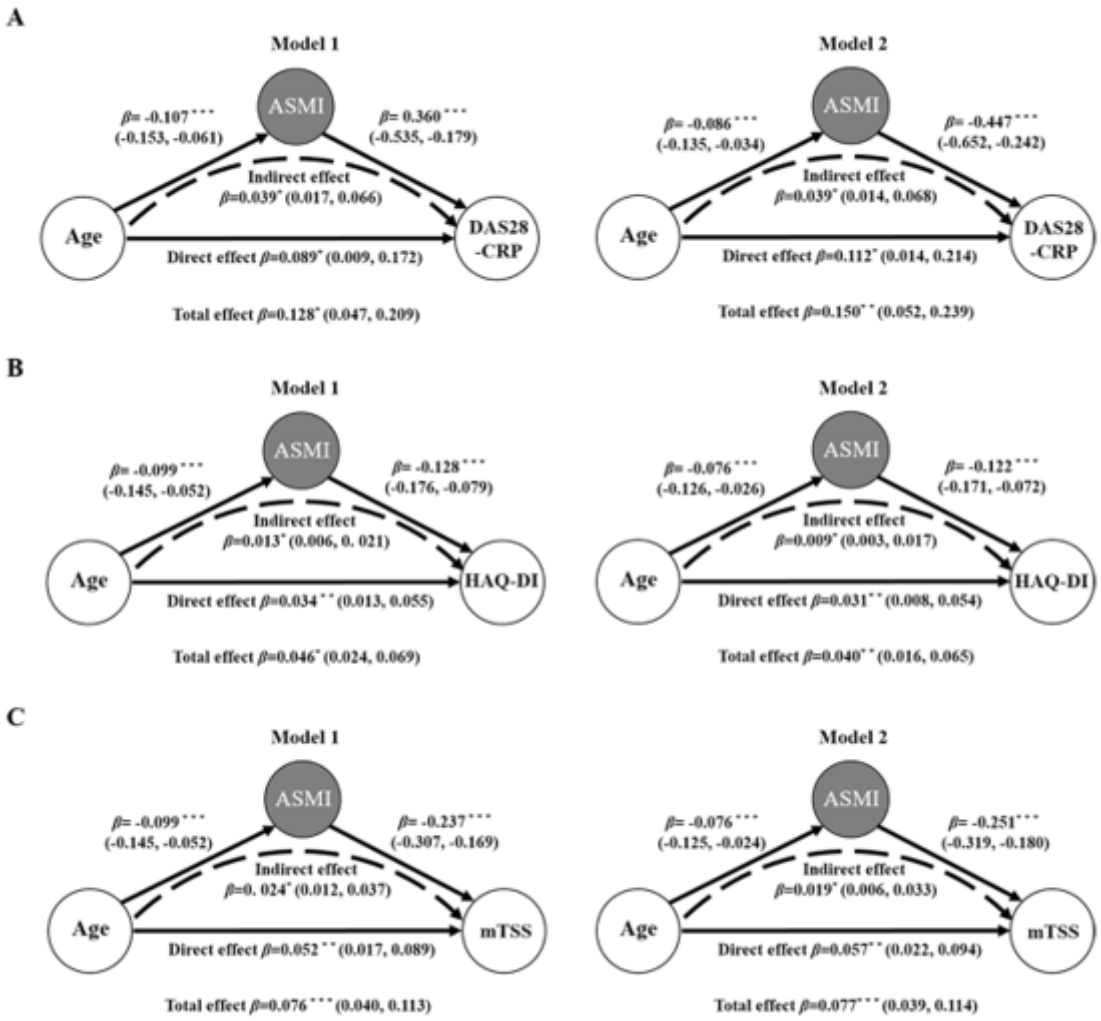

Figure 2

Mediation analysis of ASMI on the associations between age and RA disease characteristics. Mediation analysis of ASMI on the associations between age and DAS28-CRP (A) which is adjusted for gender, disease duration, BMI, active smoking, RF status, ACPA status and previous medications (model 1) or comorbidities (model 2). Mediation analysis of ASMI on the associations between age and HAQ-DI (B), mTSS (C) which is adjusted for gender, disease duration, BMI, active smoking, RF status, ACPA status, DAS28-CRP and previous medications (model 1) or comorbidities (model 2). Number of bootstrap samples for bias corrected bootstrap confidence interval: 10,000. Bias-corrected 95% confidence intervals were showed within parentheses. Significances are shown in bold. β, regression coefficient. *P < 0.05, **P < 0.01, ***P < 0.001.

Table 4

Linear regression analysis of age and ASMI associated with RA disease characteristics

Independent variables	Dependent variables	Univariate	Multivariate model 1△	Multivariate model 2#
		β (95%CI)	β (95%CI)	β (95%CI)
Age	DAS28-CRP	0.157 (0.064, 0.250)**	0.108 (0.017 ~ 0.199)*	NA
	HAQ-DI†	0.082 (0.054, 0.111)***	0.065 (0.035 ~ 0.095) ***	0.041 (0.019 ~ 0.063)***
	mTSS§	0.090 (0.055, 0.126)***	0.085 (0.049 ~ 0.121)***	0.077 (0.041 ~ 0.113)***
ASMI	DAS28-CRP	-0.244 (-0.370, -0.118) ***	-0.369 (-0.550~ -0.188) ***	NA
	HAQ-DI†	-0.117 (-0.156, -0.078) ***	-0.220 (-0.278~ -0.161) ***	-0.139 (-0.182~ -0.095) ***
	mTSS§	-0.197 (-0.244, -0.150) ***	-0.284 (-0.355~ -0.213)***	-0.261 (-0.332~ -0.190) ***

Data were showed in unstandardized coefficients (95% CI). NA: Not applicable.

†HAQ-DI were normalized by a natural square root transformation.

§mTSS was normalized by a lg(X + 1) transformation.

△Adjusted for gender, disease duration, active smoking, BMI, RF status, ACPA status, previous medications (categorized by treatment naïve, glucocorticoids, csDMARDs and bDMARDs therapy), and comorbidities (including hypertension, diabetes, dyslipidemia, fatty liver and heart disease).

#Adjusted for gender, disease duration, active smoking, BMI, RF status, ACPA status, previous medications, comorbidities and DAS28-CRP.

*P < 0.05, **P < 0.01, ***P < 0.001.