ORIGINAL ARTICLE

Glucocorticoid use is an independent risk factor for developing sarcopenia in patients with rheumatoid arthritis: from the CHIKARA study

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Abstract

Introduction Patients with rheumatoid arthritis (RA) are at higher risk of sarcopenia because of joint dysfunction and chronic inflammation. The present study aimed to investigate the predictors or risk factors for developing sarcopenia in RA patients using the prospective observational CHIKARA database. We hypothesized that older age, higher disease activity, lower physical function, and glucocorticoid (GC) use are risk factors for sarcopenia.

Methods A total of 100 consecutive RA patients participated in the CHIKARA study. Their body compositions were examined using a body composition analyzer. Laboratory data, disease activity, physical function, and treatment were investigated. Sarcopenia was assessed at baseline and at 1 year. Predictors or risk factors for sarcopenia development at 1 year were investigated by univariate and multivariate analyses.

Results Of 68 patients without sarcopenia at baseline, 9 (13.4%) developed sarcopenia over the year. Univariate analysis showed that age ($r = 0.28$, $p = 0.022$), average GC dose over the year ($r = 0.25$, $p = 0.043$), and body mass index ($r = -0.28$, $p = 0.019$) were significantly associated with the development of sarcopenia. Average GC use at ≥ 3.25 mg/day was a significant factor on multivariate analysis (odds ratio 8.81, 95% confidence interval 1.14–67.9, $p = 0.037$).

Conclusions RA patients using GCs at an average dose ≥ 3.25 mg/day over 1 year were at higher risk for developing sarcopenia. Reduction or withdrawal of GCs may prevent sarcopenia.

Key Points
• *Patients with RA are at higher risk of sarcopenia.*
• *Predictors or risk factors for developing sarcopenia over 1 year in RA patients were investigated using the prospective observational CHIKARA database.*
• *RA patients using GCs at an average dose ≥ 3.25 mg/day over 1 year were at higher risk for developing sarcopenia.*
• *Reduction or withdrawal of GCs may be essential to prevent sarcopenia.*

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder characterized by polyarthritis. The advent of biological disease-modifying anti-rheumatic drugs (bDMARDs) has led to a paradigm shift in RA treatment. Disease activity can be well-controlled by the treat-to-target (T2T) concept, and quality of life has improved in RA patients [1]. On the other hand, some patients still have dysfunction due to the inflammation and joint destruction. These conditions may induce sarcopenia, defined by a loss of muscle mass, strength, and function [2].

It is known that RA patients have lower muscle mass and higher fat mass, as well as metabolic disorders, including insulin resistance and dyslipidemia [3–8]. Possible reasons for these are the following: disuse due to pain or joint destruction; the inflammatory condition known as "cachexia";

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glucocorticoid (GC) use; and malnutrition. Previous cohort studies showed that RA patients had lower muscle mass and a higher prevalence of sarcopenia [9–11]. Sarcopenia decreases activities of daily living (ADL) and leads to osteoporosis, falls, fractures, and deaths [12–18]. Therefore, predicting and preventing sarcopenia are important in RA patients. However, how patient characteristics, including disease activity or treatment, affect muscle mass or the development of sarcopenia in RA patients in the era of T2T remains unclear. Sarcopenia can be easily assessed, because muscle mass is measurable by the bioelectrical impedance analysis (BIA) method using a body composition analyzer without exposure to radiation. Both the criteria of the European Working Group on Sarcopenia in Older People (EWGSOP) and the Asia Working Group for Sarcopenia (AWGS), which are frequently used to diagnose sarcopenia, include muscle mass measured by the BIA method [19, 20]. Muscle mass measured by BIA correlates with that measured by dual-energy X-ray absorptiometry (DXA).

We started the prospective observational CHIKARA study (Correlation research of sarcopenia, skeletal muscle and disease activity in rheumatoid arthritis) in 2016 to investigate correlations between sarcopenia and RA disease activity. The presence of sarcopenia, disease activity, physical function, laboratory data, and body composition at baseline and one year later were investigated in the CHIKARA study. The present study aimed to identify the patients who developed sarcopenia at one-year follow-up and to investigate the predictors or risk factors for developing sarcopenia using the CHIKARA database.

Materials and methods

Study design

The CHIKARA study is a prospective, single-center, observational cohort study that was started in 2016. Registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (registration number: UMIN000023744), this study was designed to evaluate associations between sarcopenia and disease activity in RA patients. A total of 100 consecutive RA patients (78 women, 22 men) at a single institution were included. All patients fulfilled the 2010 American College of Rheumatology/ European League Against Rheumatism classification criteria [21] and were treated based on the T2T concept. Patients with conditions that may affect muscle mass or sarcopenia (e.g., patients with severe renal failure or with a history of metal implant surgery) were excluded. After excluding 5 patients lost to follow-up at one year (3 dropped out of their own volition, 1 dropped out due to entering a geriatric health service institution, and 1 dropped out due to moving), 95 patients were finally eligible for the present study (Fig. 1). The institutional review boards approved the study protocol, and informed consent for participation in this study was obtained from all patients in accordance with the Declaration of Helsinki.

Study measures

Patient data regarding age, disease duration, Steinbrocker stage and class, and medication status [methotrexate (MTX), GCs, bDMARDs, and target synthetic DMARDs (tsDMARDs)] were recorded at baseline. As for GCs, the average dose at baseline and at 1-year follow-up was calculated. The clinical data, including laboratory data and disease activity, were collected at baseline and at one year. Regarding laboratory data, C-reactive protein (CRP), matrix metalloproteinase 3 (MMP-3), anti-cyclic citrullinated peptide antibody (ACPA), and rheumatoid factor (RF) were examined. For disease activity, the Disease Activity Score 28-joint count erythrocyte sedimentation rate (DAS28-ESR) was calculated. For functional status, the modified Health Assessment Questionnaire (mHAQ) scores were measured. Changes of these parameters at one year from baseline were also investigated. All patients provided information about falls and fractures.

In addition, body composition, including weight, body mass index (BMI), muscle mass, body fat mass, total body water, and estimated bone mass, and basal metabolic rate were measured using a body composition analyzer (MC-780A; TANITA, Tokyo, Japan) at baseline and at one year. Muscle mass was measured for the whole body and for five regions (left arm, right arm, left leg, right leg, and trunk) using two different frequencies. The electrical signal passes quickly through muscle tissue, which is relatively hydrated, whereas it meets resistance through fat tissue. Each body composition was calculated based on this "impedance" difference in the BIA method. Changes in body composition at one year from baseline were also assessed.

Assessing sarcopenia development

The appendicular skeletal muscle mass index (ASMI) was calculated to assess the muscle mass (sum of the arms and legs' lean mass divided by the square of the height). Gait speed (distance per second) was calculated on a 3-m walk test as a measure of muscle function. Furthermore, grip strength was measured as an indicator of muscle strength using a digital hand-held isokinetic dynamometer (TKK-5401; Takei Scientific Instruments, Niigata, Japan). Sarcopenia was diagnosed using the AWGS criteria [19]. Pre-sarcopenia was defined as ASMI $< 7.0 \ \text{kg/m}^2$ in men and $< 5.7 \ \text{kg/m}^2$ in women. Patients with pre-sarcopenia with a gait speed of less than 0.8 m/s (low muscle function) or grip strength less than
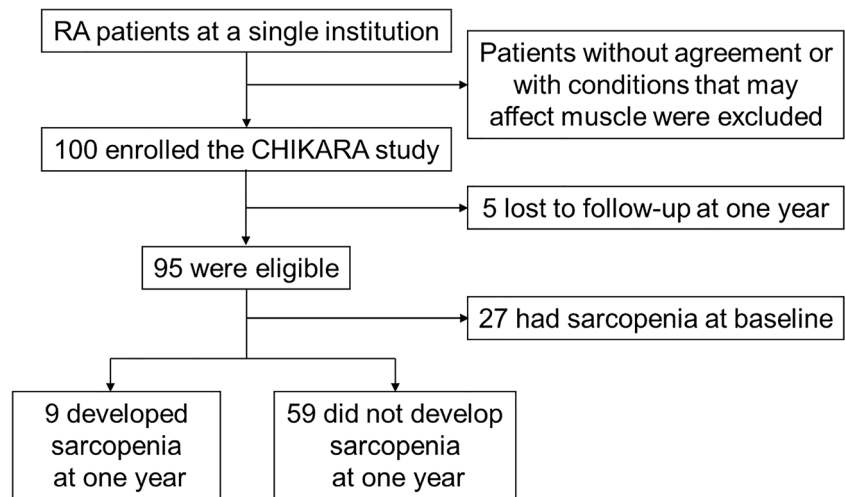
26 kg in men or 18 kg in women (low muscle strength) were diagnosed as having sarcopenia. The presence of sarcopenia was assessed at baseline and at one year in 95 participants.

Among patients without sarcopenia at baseline, those with and without sarcopenia development at one year were compared. Associations between sarcopenia development and patients' characteristics, including disease activity (DAS28-ESR), medication status (MTX, GCs, bDMARDs), physical function (mHAQ), body composition (ASMI, fat mass, etc.), and laboratory data (CRP, MMP-3, etc.), at baseline and their changes at one year from baseline (Δ) were investigated.

Statistical analysis

The characteristics of patients with and without sarcopenia development are described as means ± standard deviation (SD) for those with a normal distribution or as medians (25th, 75th percentiles) for those not normally distributed. The difference between the two groups was analyzed using Student's t test or the Mann–Whitney U test for continuous data and the chi-squared test for categorical data. Associations between sarcopenia development and patients' characteristics at baseline or changes at one year (Δ) were investigated using Spearman's correlation coefficients on univariate analyses. Receiver operating characteristic (ROC) curve analysis for average GC dose and sarcopenia development was performed to treat GC dose as a categorical value, and the cut-off value was calculated using the Youden index to maximize the sum of sensitivity and specificity. The odds ratios (ORs) and 95% confidence intervals (CIs) for sarcopenia development were calculated by the forced entry method using age, disease activity, physical function, and GC dose as explanatory variables, which were considered to be clinically relevant on multivariate logistic analysis. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). P values < 0.05 were considered significant.

Results

Patient characteristics at baseline

A total of 27 patients had sarcopenia at baseline (Fig. 1). Table 1 shows the demographics and disease characteristics of the 68 participants without sarcopenia at baseline. The median age was 66.0 years (80.9% female), and the median disease duration was 5.7 years. About one-third of the patients had advanced joint destruction, defined by Steinbrocker stage III or IV. Almost all patients maintained higher functional activity, defined by Steinbrocker functional class 1 or 2, and the median mHAQ was 0.25. Disease activity was moderate: the median DAS28-ESR was 3.52. Most patients (89.6%) were treated with MTX, 29.4% with GCs, and 33.8% with bDMARDs (golimumab, $n = 5$; tocilizumab, $n = 3$; infliximab, $n = 3$; abatacept, $n = 3$; etanercept, $n = 3$; adalimumab, $n = 3$; certolizumab pegol, $n = 1$) or tsDMARDs (tofacitinib, $n = 2$).

Patients who developed sarcopenia

Of the 68 patients without sarcopenia at baseline, 9 (13.4%) developed sarcopenia over the year. They were significantly older than patients without sarcopenia (76 (70, 80) and 66 (59, 73) years, respectively; $p = 0.024$). They also had lower BMI (20.8 ± 2.1 and 23.2 ± 3.4 kg/m^2, respectively; $p = 0.040$) and body fat mass (11.7 ± 3.8 and 17.6 ± 6.9 kg/m^2, respectively; $p = 0.015$). GC use was more frequent in patients who developed sarcopenia (55.6%) than in those who did not (25.4%), but there was no significant difference between the two groups ($p = 0.064$) (Table 1). Other baseline data, including

Table 1 Baseline demographics, characteristics, and their changes at 1-year follow-up in all RA patients without sarcopenia at baseline and those with and without sarcopenia at 1 year

	All patients without sarcopenia at baseline ($n = 68$)	Sarcopenia development ($n = 9$)	Non-sarcopenia development ($n = 59$)	P value
Women (%)	80.9	66.7	83.1	0.244§
Age (years)	66 (59, 74)	76 (70, 80)	66 (59, 73)	0.024‡
Disease duration (years)	5.7 (1.1, 10.5)	7.4 (2.0, 13.5)	5.3 (1.1, 10.3)	0.333‡
Stage I/II/III/IV	27/21/10/10	2/2/3/2	25/19/7/8	0.273§
Class 1/2/3/4	33/32/3/0	3/5/1/0	30/27/2/0	0.426§
CRP (mg/dl)	0.10 (0.04, 0.26)	0.30 (0.15, 0.58)	0.10 (0.04, 0.22)	0.106‡
MMP-3 (ng/ml)	68.9 (51.8, 105.4)	83.7 (70.7, 158.9)	64.6 (50.6, 101.6)	0.135‡
DAS28-ESR	3.52 ± 0.90	3.65 ± 1.00	3.50 ± 0.89	0.641†
mHAQ	0.25 (0.13, 0.63)	0.50 (0.13, 1.38)	0.25 (0.06, 0.50)	0.094‡
MTX use rate (%)	89.6	100.0	87.9	0.347§
MTX dose (mg/week)	8.4 ± 2.9	7.2 ± 3.2	8.6 ± 2.8	0.192†
GC use rate (%)	29.4	55.6	25.4	0.064§
GC dose at baseline (mg/day)	3.9 ± 1.8	3.9 ± 1.5	4.0 ± 1.9	0.957†
Average GC dose (mg/day)	3.0 ± 1.8	3.5 ± 1.6	2.8 ± 1.9	0.530†
bDMARD or tsDMARD use rate (%)	33.8	33.3	33.9	0.973§
BMI (kg/m^2)	22.9 ± 3.4	20.8 ± 2.1	23.2 ± 3.4	0.040†
Fat percentage (%)	29.5 ± 8.4	23.5 ± 7.4	30.4 ± 8.2	0.019†
Muscle mass (kg)	34.7 (33.1, 39.3)	32.6 (31.4, 41.3)	35.0 (33.3, 38.7)	0.370‡
Estimated bone mass (kg)	2.1 (1.9, 2.4)	1.9 (1.7, 2.3)	2.1 (1.9, 2.4)	0.275‡
Basal metabolic rate (kcal)	1081 (1002, 1197)	986 (929, 1149)	1084 (1029, 1198)	0.164‡
SMI (kg/m^2)	6.72 ± 0.74	6.38 ± 0.67	6.77 ± 0.74	0.134†
ΔCRP (mg/dl)	0.00 (− 0.08, 0.14)	− 0.12 (− 0.39, 0.00)	0.00 (− 0.03, 0.16)	0.018‡
ΔMMP-3 (mg/dl)	1.0 (− 10.6, 18.0)	− 1.5 (− 12.6, 67.3)	2.5 (− 10.2, 17.6)	0.979‡
ΔDAS28-ESR	− 0.42 (− 0.88, 0.01)	− 0.54 (− 0.60, − 0.21)	− 0.41 (− 0.92, 0.02)	0.738‡
ΔmHAQ	0 (− 0.13, 0.25)	0 (− 0.13, 0.38)	0 (− 0.13, 0.25)	0.978‡

Data are shown as mean ± standard deviation (SD) or median (25th, 75th percentile). Baseline demographics, characteristics, and their changes at a year of those with and without sarcopenia development were compared. Continuous variables were analyzed using an unpaired Student's t test† or the Mann–Whitney U test‡. Categorical variables were analyzed using chi-squared test§

RA, rheumatoid arthritis; CRP, C-reactive protein; MMP-3, matrix metalloproteinase 3; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; mHAQ, modified Health Assessment Questionnaire; MTX, methotrexate; GC, glucocorticoid; bDMARD, biological disease-modifying antirheumatic drug; tsDMARD, targeted synthetic disease-modifying antirheumatic drug; BMI, body mass index; SMI, skeletal muscle index

laboratory data, bDMARD use, and disease activity, showed no significant differences between the two groups.

Factors associated with sarcopenia development

Factors associated with sarcopenia development on univariate analysis are shown in Table 2. Age ($r = 0.28$, $p = 0.022$), average GC dose ($r = 0.25$, $p = 0.043$), BMI ($r = -0.28$, $p = 0.019$), body fat mass ($r = -0.34$, $p = 0.005$), and ΔCRP ($r = -0.205$, $p = 0.046$) were significantly associated with sarcopenia development, although these associations were not strong. Baseline GC dose ($r = 0.22$, $p = 0.072$) and mHAQ ($r = 0.21$, $p = 0.092$) tended to be associated with sarcopenia development. DAS28-ESR ($r = 0.07$, $p = 0.508$), ΔDAS28-ESR ($r = -0.03$, $p = 0.757$), MTX use ($r = -0.001$, $p = 0.989$), and bDMARD use ($r = 0.02$, $p = 0.850$) showed no associations with sarcopenia development.

Analysis of the ROC curve for average GC dose over the year and sarcopenia development showed that the cut-off value of GC dose was 3.25 mg/day, and the area under the ROC curve (AUC) was 0.67 (95% CI: 0.47–0.86) (Fig. 2). On multivariate logistic analysis, average GC use ≥ 3.25 mg/day (OR 8.81, 95% CI 1.14–67.9, $p = 0.037$) was identified as a significant factor for developing sarcopenia, when average GC use, age, mHAQ, and DAS28-ESR were used as explanatory variables (Table 2). These variables did not show multicollinearity.

Table 2 Univariate and multivariate analyses of predictors or risk factors for developing sarcopenia in RA patients

|	Univariate		Multivariate		
	R value	P value	OR	95% CI	P value
Age	0.28	0.022	1.08	0.99–1.18	0.083
Disease duration	0.12	0.332	–	–	–
MTX use	−0.05	0.664	–	–	–
Baseline GC dose	0.22	0.072	–	–	–
Baseline GC use	0.22	0.066	–	–	–
Average GC dose	0.25	0.043	–	–	–
Average GC dose ≥ 3.25 mg/day	0.40	< 0.001	8.81	1.14–67.9	0.037
bDMARD or tsDMARD use	−0.004	0.974	–	–	–
DAS28-ESR	0.10	0.414	0.59	0.18–1.91	0.379
mHAQ	0.21	0.092	1.00	1.00–1.00	0.364
BMI	−0.28	0.019	–	–	–
Body fat mass	−0.34	0.005	–	–	–
SMI	−0.22	0.067	–	–	–
ΔCRP	−0.29	0.016	–	–	–
ΔMMP-3	0.004	0.972	–	–	–
ΔDAS28-ESR	−0.04	0.734	–	–	–
ΔmHAQ	0.005	0.971	–	–	–

We performed multivariate logistic regression analysis using age, DAS28-ESR and mHAQ and average GC dose ≥ 3.25 mg/day as explanatory variables

RA, rheumatoid arthritis; OR, odds ratio; CI, confidence interval; GC, glucocorticoid; bDMARD, biological disease-modifying antirheumatic drug; tsDMARD, targeted synthetic disease-modifying antirheumatic drug; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; BMI, body mass index; SMI, skeletal muscle index; CRP, C-reactive protein; MMP-3, matrix metalloproteinase 3; mHAQ, modified Health Assessment Questionnaire; Δ, changes from baseline

Discussion

The relationships of disease activity and treatment with sarcopenia at one-year follow-up were investigated in RA patients. Overall, 13.4% of RA patients in the present cohort developed sarcopenia over a 1-year period, and average GC dose ≥ 3.25 mg/day over the year was an independent risk factor for the development of sarcopenia.

The previous studies reported that the prevalence of sarcopenia in RA patients was 25.9–43.3% [10, 22–25]. We have already reported that the prevalence of sarcopenia in RA patients was 28% at baseline in this study [9]. This is higher than in the community-dwelling general population (22.7%) in a Japanese database [26]. This can be explained by the fact that muscle mass decreases, as well as bone mass, whereas fat mass increases or is not changed in RA patients [4, 27, 28]. RA patients are at higher risk for sarcopenia because of disuse due to pain or joint destruction, the inflammatory condition known as "cachexia," GC use, and malnutrition. Matsumoto et al. reported that sarcopenic patients with RA had low BMI, high disease activity, low body function (high mHAQ score), and low intake of dairy products [29]. Torii et al. reported that age, longer disease duration, joint destruction, malnutrition, and bDMARD use were associated with sarcopenia on
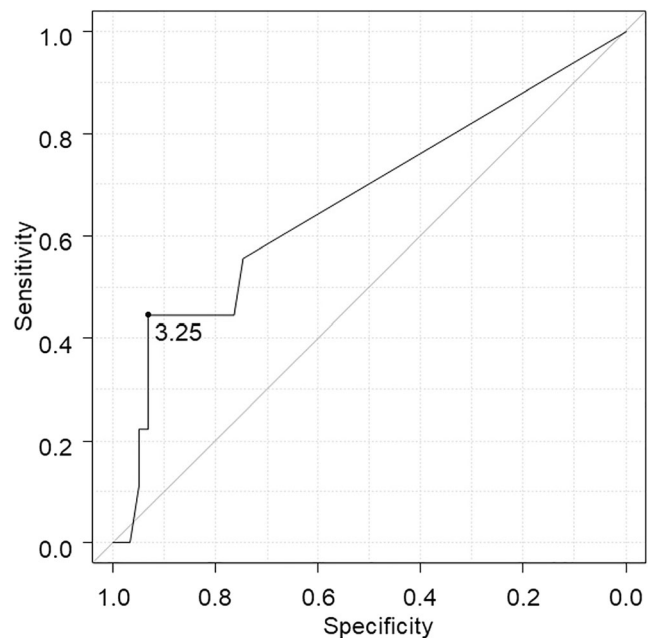
Fig. 2 Receiver operating characteristic (ROC) curve analysis for average GC dose in relation to sarcopenia development. The cut-off value of the average GC dose is 3.25 mg/day, and the area under the ROC curve (AUC) is 0.67 (95% CI: 0.47–0.86)

multiple linear logistic regression analysis in a cross-sectional observational study. They also showed that GC use was significantly more frequent in those with sarcopenia than in those without [10]. Based on these, the risk factors for sarcopenia in RA patients are considered to include older age, high disease activity, low body function, and GC use. However, the predictors or risk factors for sarcopenia development in patients with RA in the era of T2T were not known, because many patients have achieved remission or low disease activity. This is the reason why we started the CHIKARA study. According to the cross-sectional evaluation of the CHIKARA study, sarcopenia was independently associated with low BMI, high fat mass, and high MMP-3 [9].

To the best of our knowledge, this study is the first to investigate sarcopenia development over time in patients with RA. Kim et al. reported that 39.6% of 538 nonsarcopenic women aged over 75 years developed sarcopenia over 4 years and that age, BMI, calf circumference, and a high cystatin-C level were predictors of sarcopenia development [30]. The present study showed a higher incidence rate (13.4% per year) of sarcopenia compared with their study. This fact indicates that RA patients are at higher risk of sarcopenia development. In the present study, average GC use, even 3.25 mg/day over the year, was an independent risk factor for sarcopenia development in RA patients. GC continuation appears to promote sarcopenia development.

It is known that RA induces the metabolic abnormality called "cachexia," which is characterized by a loss of skeletal muscle due to chronic inflammation [3–5]. Sarcopenia is induced by aging, disuse, endocrine disorders, and cachexia [20]. Since RA patients often have disuse due to joint destruction, cachexia due to inflammation, and endocrine disorders induced by GC use, they are considered to be at a higher risk for developing sarcopenia. Kramer et al. reported that GC use was associated with a loss of muscle mass because GC use not only redistributes fat from the periphery to the trunk but also induces muscle wasting [31]. Such "steroid myopathy" is a well-known side effect of GCs. In the present study, GC use was an independent risk factor for developing sarcopenia, although GCs have an anti-inflammatory effect. This suggests that GCs reduce muscle mass rather than exert an anti-inflammatory effect.

It is known that inflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin-6 (IL-6), have a protein-catabolic effect on the muscle, so that the prevalence of sarcopenia is higher in RA patients, especially with high disease activity [6, 32, 33]. In addition, these body composition changes including sarcopenia were reversed by bDMARD use, since these agents inhibit the inflammatory cytokines [22]. As previously described, bDMARD use was associated with sarcopenia in a cross-sectional observational study [10]. However, there was no relationship between disease activity or bDMARD use and sarcopenia development in

the present study, contrary to expectations. This is probably because there were few participants with high disease activity under the T2T concept. In fact, DAS28-ESR, CRP, and MMP-3 did not change greatly over the year of follow-up. The mean ΔDAS28-ESR was − 0.41, the mean ΔCRP was 0.00 mg/dl, and the mean ΔMMP-3 was − 1.6 ng/ml. Another recent study also found no relationship between disease activity and sarcopenia [23, 24].

There are some limitations in this study. First, there may have been selection bias. Few participants with low ADL defined by Steinbrocker class 3 or 4, often showing "rheumatoid cachexia" or "sarcopenic obesity" due to intensive inflammation, were included. Disease activity was not found to be a predictor for developing sarcopenia, but this result may have been different if the participants had included RA patients with high disease activity. Second, there were few new cases of sarcopenia because of the small number of participants and the short-term follow-up. In fact, the ROC curve analysis for average GC dose in relation to sarcopenia development showed low predictive ability (AUC 0.67), although GC dose ≥ 3.25 mg/day was associated with sarcopenia development on univariate and multivariate analyses. We will continue further follow-up and assessments for sarcopenia development.

In conclusion, the present study showed that average GC dose ≥ 3.25 mg/day over the year was an independent risk factor for developing sarcopenia in RA patients (OR 8.11). Reduction or withdrawal of GCs, as well as controlling disease activity by the T2T concept, may prevent sarcopenia development.

Compliance with ethical standards

Disclosures None.

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