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Original article

Osteosarcopenia synergistically increases the risk of falls in patients with rheumatoid arthritis

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ABSTRACT

Objectives: Osteosarcopenia is defined as osteoporosis with sarcopenia. The impacts of osteosarcopenia on falls and fractures in rheumatoid arthritis (RA) patients were investigated using 4 years of data from a longitudinal study (CHIKARA study).
Methods: The patients were divided into 4 groups by their baseline status: no sarcopenia and no osteoporosis (SP-OP-); only sarcopenia (SP + OP-); only osteoporosis (SP-OP+); and both sarcopenia and osteoporosis (SP + OP+). Survival rates and Cox hazard ratios were analyzed using falls and fractures as endpoints, adjusted by age, sex, and body mass index.
Results: A total of 100 RA patients (SP-OP-: 44%, SP + OP-: 17%, SP-OP+: 28%, and SP + OP+: 11%) were enrolled; 37 patients had falls, and 19 patients had fractures. The fall-free and fracture-free survival rates were significantly lower in SP + OP+ (36.4%, 54.5%) than in SP-OP- (75.0%, 86.4%). The hazard ratio of falls was significantly increased in SP + OP+, by 3.32-fold (95%CI: 1.01–10.9), whereas in SP + OP- and SP-OP+, there were no differences compared to SP-OP-.
Conclusions: The survival rates with the endpoints of falls and fractures in RA patients with osteosarcopenia were lower during 4-year follow-up. The risk of falls increased with the synergistic effect of osteoporosis and sarcopenia.

1. Introduction

The number of elderly people is increasing rapidly in the world with the improvement of sanitation and increased health consciousness. In particular, the population aging rate of Japan is the highest in the world. The increase of elderly people and of elderly onset has become obvious in patients with rheumatoid arthritis (RA). Osteoporosis and sarcopenia are frequently diagnosed in elderly people and lead to frailty due to functional disability and weakness in activities of daily living [1,2]. Osteosarcopenia has recently been reported to be a new syndrome of the co-existence of osteoporosis and sarcopenia. The prevalence of sarcopenia was 25% for those with osteopenia and 50% for those with osteoporosis in postmenopausal women. Muscle and bone are a musculoskeletal unit that interact with each other via fat [3,4].

Osteoporosis and sarcopenia are independent risk factors for fractures and falls, respectively. These patients are at significantly higher risk of falls, fractures, and institutionalization [5], and they have a significantly higher mortality rate than patients with osteoporosis or sarcopenia alone [6]. The risks of falls and fractures were significantly higher in patients with osteosarcopenia than in those having only osteoporosis or sarcopenia. The synergistic effect of osteoporosis and sarcopenia has been reviewed [2]. We previously reported that bone mineral density (BMD) and bone

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metabolic markers of patients with RA were significantly less than those of a healthy control group in a prospective cohort study (TOMORROW study) [7,8]. In addition, we reported that the prevalence of sarcopenia was 28%, and matrix metalloproteinase 3 (MMP3) was an independent risk factor for sarcopenia in patients with RA from the CHIKARA study [9]. However, there were no correlations among falls, fractures, and sarcopenia with 1-year follow-up in our study. Therefore, muscle functions including power, speed, and balance were important to predict falls and fractures in longitudinal analysis [10].

There has been no report of the prevalence of osteosarcopenia, and its synergistic effect on falls and fractures in patients with RA is unknown. The synergistic effect of osteoporosis and sarcopenia and the impact of osteosarcopenia on falls and fractures in patients with RA were investigated using 4 years of data from a longitudinal study.

2. Methods

2.1. Study design and patients

A prospective, observational study was conducted from 2016 to identify correlations of sarcopenia, locomotive syndrome, and RA disease activity, as the correlation research of sarcopenia, skeletal muscle and disease activity in rheumatoid arthritis (CHIKARA) study [9], which is registered with the UMIN Clinical Trials Registry [http://www.umin.ac.jp/ctr/] (UMIN000023744). One hundred consecutive patients with RA seen in the outpatient clinic at our hospital were studied. All patients fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria [11], and their age was over 20 years. Exclusion criteria were severe renal dysfunction, heart failure, neurological diseases, malignancy, other collagen disease (systemic lupus erythematosus, polymyalgia rheumatica), myogenic disease (myasthenia gravis, amyotrophic lateral sclerosis), or surgically implanted metal. The details were described in the previous report [9]. During the 4-year follow-up, 15 cases dropped out: 10 due to personal choice, 4 due to relocation, and 1 who entered a retirement home. This study protocol (IRB approval number: 1505019) was approved by the institutional review committee of our hospital. In accordance with the Declaration of Helsinki, written, informed consent for participation in the study was obtained from all participants. Correlations between osteosarcopenia and the patients' numbers of falls and fractures were investigated by longitudinal analysis using the baseline and four-year follow-up data of the CHIKARA study.

2.2. Definitions of osteoporosis, sarcopenia, and osteosarcopenia

Sarcopenia was defined according to the Asia Working Group for Sarcopenia (AWGS) 2014 criteria [12]. Osteoporosis was defined according to the Japanese Guidelines for Prevention and Treatment of Osteoporosis 2011 [13]. These criteria defined osteoporosis as under 70% young adult mean (YAM) without a past fragility fracture or under 80% YAM with a past fragility fracture. YAM 70% was equally T-score −2.5SD by BMD. Lumbar spine (L2-4) and proximal femur bone (total and neck) BMD were measured by dual-energy X-ray absorptiometry (DXA) (Hologic Discovery: Hologic, Inc., Marlborough, MA, USA). The approximate coefficients of variance were 1%. Osteosarcopenia was defined as fulfilling both definitions. All patients were divided into 4 groups according to their baseline status: no sarcopenia and no osteoporosis (SP-OP-); only sarcopenia (SP + OP-); only osteoporosis (SP-OP+); and both sarcopenia and osteoporosis (SP + OP+).

2.3. Evaluation of sarcopenia

Body composition was measured by a body composition analyzer (MC-780A; TANITA, Tokyo, Japan). This device was able to measure weight, fat mass, muscle mass, estimated bone mass, basal metabolic rate, and total body water for the trunk and extremities. Grip strength was evaluated using a digital hand-held isokinetic dynamometer (TKK-5401; Takei Scientific Instruments, Niigata, Japan). The higher value was adopted after measuring both arms. Gait speed was measured by the 3-m walk test. Sarcopenia was diagnosed if the appendicular skeletal mass index (ASMI) was less than 7.0 kg/m^2 in men and less than 5.7 kg/m^2 in women, and grip strength was less than 26 kg in men and less than 18 kg in women or gait speed was less than 0.8 m/s [12].

2.4. Assessments of clinical status

Each patient was treated with a treatment strategy based on the treat-to-target (T2T) concept [14] by their physician for the entire duration of this study. Anti-cyclic citrullinated peptide antibody (ACPA), rheumatoid factor (RF), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and MMP3 were evaluated by laboratory examinations. The disease activity score (DAS) composite of the ESR and the 28-joint score (DAS28-ESR) [15] and Simplified Disease Activity Index (SDAI) [16] were calculated to assess disease activity. Modified health assessment questionnaire (mHAQ) scores [17] were used to evaluate activities of daily living and quality of life. Drugs prescribed for RA, osteoporosis, and comorbidities were investigated from the medical records.

2.5. Assessments of falls and fractures

A fall was defined as the subject unintentionally coming to rest on the ground or at a lower level [18]; the definition of fall included slipping from a bed or chair. The patients kept a diary to record falls and fractures, and falls and fractures were investigated annually by interview, and the X-ray was checked by the physician in doubtful cases. The patients' numbers of falls and fractures during the 4-year follow-up period were counted, and the fracture sites were recorded.

2.6. Statistical analysis

All data are presented as means ± standard deviation (SD) or medians (25th, 75th percentile). Differences in clinical variables, laboratory data, body composition, and the patients' numbers of falls and fractures among the 4 groups were analyzed using the Kruskal-Wallis test adjusted by the Bonferroni correction for continuous variables and Fisher's exact test for categorical variables. The fall-free and fracture-free survival rates of the 4 groups were calculated and compared by the log-rank test adjusted by the Bonferroni correction. The hazard ratios of falls and fractures were evaluated by Cox proportional hazards models, adjusted by age, sex, and body mass index (BMI), which were previously reported to be associated with falls and fractures. The hazard ratios were calculated compared to the SP-OP- group. Correlations between disease activity, glucocorticoid (user and dosage) and body composition components (muscle mass and bone mass) and fall and fracture events during 4-year follow-up were examined using Spearman's correlation coefficients. All statistical tests were two-tailed, and values of $P < 0.05$ were considered significant. When the Bonferroni correction was used for multiple comparisons in the 4 groups, values of $P < 0.0083$ were considered significant. All statistical analyses were analyzed using IBM SPSS Statistics version 26.0 (IBM, Armonk, NY, USA).

3. Results

3.1. Prevalence of sarcopenia, osteoporosis, and osteosarcopenia

The percentages of SP-OP-, SP + OP-, SP-OP+, and SP + OP+ were 44%, 17%, 28%, and 11% in the total 100 patients. The characteristics of RA and body composition at baseline are shown in Table 1. There were significantly fewer women in the SP + OP- group (58.8%) than in the other groups. Age was significantly higher in the SP-OP + group (73 years), and disease duration was significantly longer in the SP + OP + group (10.5 years) compared with the SP-OP- group. The MMP3 level was the highest among the 4 groups in the SP + OP- group (117.4 ng/ml). The DAS28-ESR was significantly higher in the SP-OP + group (4.03) than in the SP-OP- (3.14) group. The same tendency was seen for the SDAI. There were no significant differences in MTX dosage and usage rate. Glucocorticoid user was 25 patients (25%) and mean dosage was 4.1 ± 1.8 mg in the whole group. The usage rate of glucocorticoid in the SP-OP + group was higher than that in the other groups. However, there were no significant differences in glucocorticoid mean dosage. The usage rate of biological disease-modifying antirheumatic drugs (bDMARDs) or targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) was from 23.5% to 32.1%; there were no significant differences among the 4 groups.

The BMI and muscle mass were significantly lower in the SP + OP- and SP + OP + groups than in the SP-OP- group. The ASMI was significantly lower in the SP + OP- and SP + OP + groups than in the SP-OP- and SP-OP + groups. The estimated bone mass was higher in the SP-OP- group (2.3 kg) than in the other groups.

3.2. Falls and fractures during the 4-year follow-up

A total of 37 patients had falls, and 19 patients had fractures during the 4-year follow-up. Fracture locations were the thoracolumbar spine (n = 5), femoral neck (n = 2), rib (n = 5), and others (n = 7). The fall rates in the SP-OP-, SP + OP-, SP-OP+, and SP + OP + groups were 25.0%, 35.3%, 46.4%, and 63.6%, respectively; there was a significant difference among the 4 groups (P = 0.029). The fracture rates in the SP-OP-, SP + OP-, SP-OP+, and SP + OP + groups were 13.6%, 17.6%, 17.9%, and 45.5%, respectively; there was no significant difference among the 4 groups (P = 0.067).

3.3. Survival rate and hazard ratio of falls

The fall-free survival rates of the 4 groups are shown in Fig. 1. That in the SP + OP + group was 36.4%, significantly lower than that in the SP-OP- group (P = 0.003). The fall-free survival rates in the SP + OP- and SP-OP + groups were 64.7% and 53.6%, respectively. There were no significant differences compared to the SP-OP- group (75.0%).

The hazard ratios of falls, adjusted by age, sex, and BMI, are shown in Fig. 2. Compared to the SP-OP- group, the hazard ratio was

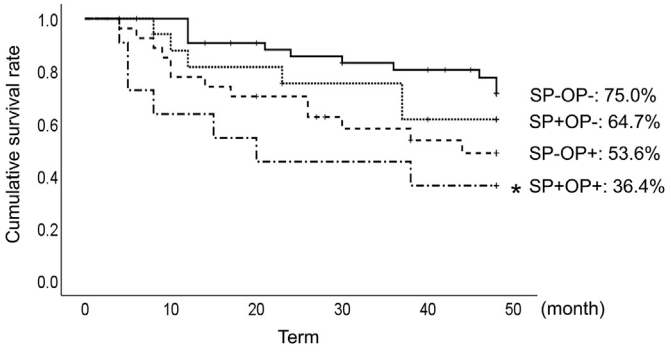

Fig. 1. Fall-free survival rates of the four groups.
There are significant differences among the 4 groups. The rate is significantly lower in the SP + OP + group than in the SP-OP- group (P = 0.003).
SP-OP-: no sarcopenia and no osteoporosis, SP + OP-: only sarcopenia, SP-OP+: only osteoporosis, SP + OP+: both sarcopenia and osteoporosis.
*: Compared among the 4 groups by the log-rank test and with the SP-OP- group with the Bonferroni correction, P < 0.0083.

Table 1
Characteristics of rheumatoid arthritis and body composition at baseline.

	SP-OP- (n = 44)	SP + OP- (n = 17)	SP-OP+ (n = 28)	SP + OP+ (n = 11)	P-value
Women, %	75.0	58.8[#]	85.7	100	0.013**
Age, yr	63 (49, 72)	69 (60, 79)	73 (65, 76)[a]	73 (65, 81)	0.001*
Disease duration, yr	4.4 (1.0, 8.6)	4.0 (1.3, 8.9)	7.5 (1.5, 14.3)	10.5 (3.2, 26.5)[a]	0.019*
Stage, I/II/III/IV	21/16/3/6	4/6/4/3	8/8/7/5	2/2/3/4	0.188**
Class, 1/2/3/4	27[#]/16/1/0	10/5/1/0	9/17/2/0	1/10[#]/1/0	0.001**
MMP3, ng/ml	62.1 (50.1, 98.2)	117.4 (96.8, 214.6)[a]	80.2 (58.9, 181.7)	90.8 (58.7, 168.5)	0.005*
DAS28-ESR	3.14 (2.66, 3.63)	3.55 (3.01, 4.65)	4.03 (3.29, 4.71)[a]	3.53 (2.48, 3.89)	0.003*
SDAI	6.6 (4.1, 12.8)	14.1 (6.7, 21.5)	15.0 (12.0, 17.9)[a]	10.2 (3.7, 13.2)	0.001*
mHAQ	0.25 (0, 0.375)	0.375 (0.125, 0.875)	0.375 (0.125, 0.875)	0.5 (0.125, 0.875)	0.065*
ACPA positive, %	75.0	88.2	82.1	72.7	0.428*
RF positive, %	59.1	82.4	67.9	45.5	0.137*
MTX user, n, %	37 (84.1)	12 (70.6)	26 (92.9)	10 (90.9)	0.216**
MTX dose, mg/week	8.2 ± 2.8	8.7 ± 3.5	8.5 ± 2.9	6.8 ± 1.0	0.365*
Glucocorticoid user, n, %	8 (18.1)	2 (11.8)	13 (46.4)[#]	2 (18.2)	0.023**
Glucocorticoid dose, mg/day	3.5 ± 1.8	6.3 ± 1.8	4.1 ± 1.8	3.8 ± 1.8	0.484*
bDMARDs or tsDMARDs, %	31.8	23.5	32.1	27.3	0.863*
Body mass index, kg/m^2	23.5 ± 3.8	19.2 ± 2.3[a]	21.6 ± 2.3	19.2 ± 2.0[a]	< 0.001*
Grip strength, kg	17.8 ± 6.5	14.3 ± 6.2	14.6 ± 5.9	13.5 ± 3.8	0.062*
Gait speed, m/s	1.4 ± 0.3	0.9 ± 0.3	1.3 ± 0.2	0.9 ± 0.1	0.082*
Muscle mass, kg	36.8 (34.4, 41.9)	33.3 (30.4, 34.6)[a]	33.2 (30.6, 39.7)	30.4 (29.0, 31.4)[a]	< 0.001*
ASMI, kg/m^2	6.9 (6.2, 7.4)	5.5 (5.3, 6.1)[ac]	6.3 (6.0, 6.9)	5.5 (5.4, 5.6)[ac]	< 0.001*
Estimated bone mass, kg	2.3 (2.0, 2.6)	1.9 (1.7, 2.3)[a]	1.9 (1.7, 2.1)[a]	1.7 (1.5, 1.7)[a]	< 0.001*

Data are shown as mean ± standard deviation (SD) or median (25th, 75th percentile).
Continuous variables were analyzed using Kruskal-Wallis test adjusted Bonferroni*. Categorical variables were analyzed using Fisher exact test**. #: different proportion, a: compared with SP-OP- group, c: compared with SP-OP + group.
MMP3, matrix metalloproteinase 3; DAS, disease activity score; ESR, erythrocyte sedimentation rate; SDAI, simplified disease activity index; mHAQ, modified health assessment questionnaire; ACPA, anti-cyclic citrullinated peptide antibody; RF, rheumatoid factor; MTX, methotrexate; bDMARDs, biological disease-modifying antirheumatic drugs; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs; ASMI: appendicular skeletal mass index.

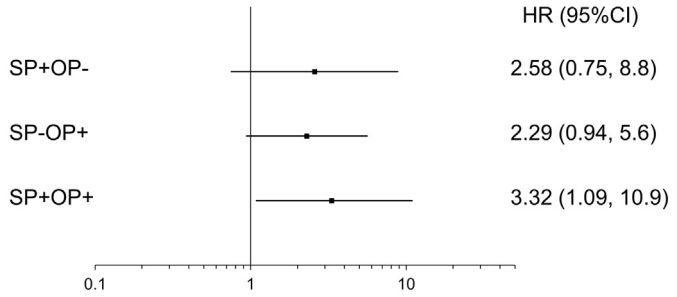

Fig. 2. Forest plots of the hazard ratio (HR) for falls.
The HR of falls was evaluated by a Cox proportional hazards model, adjusted by age, sex, and body mass index. With the HR of falls in the SP-OP- group set at 1, the HRs of the SP + OP-, SP-OP+, and SP + OP + groups were calculated.
CI: confidence interval, SP-OP-: no sarcopenia and no osteoporosis, SP + OP-: only sarcopenia, SP-OP+: only osteoporosis, SP + OP+: both sarcopenia and osteoporosis.

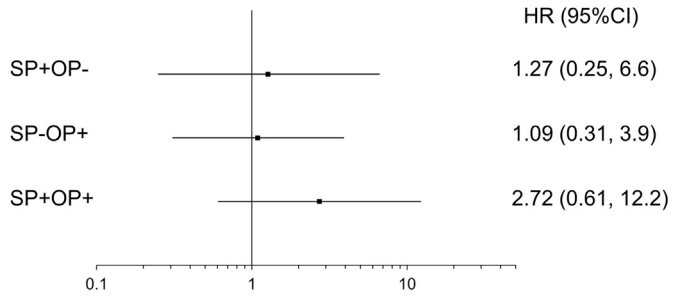

Fig. 4. Forest plots of the hazard ratio (HR) for fractures.
The HR of fractures was evaluated by a Cox proportional hazards model, adjusted by age, sex, and body mass index. With the HR of fractures in the SP-OP- group set at 1, the HRs of the SP + OP-, SP-OP+, and SP + OP + groups were calculated.
CI: confidence interval, SP-OP-: no sarcopenia and osteoporosis, SP + OP-: only sarcopenia, SP-OP+: only osteoporosis, SP + OP+: both sarcopenia and osteoporosis.

significantly increased in the SP + OP + group by 3.32-fold (P = 0.048), whereas the hazard ratios were not significantly increased in the SP + OP- and SP-OP + groups (P = 0.132 and P = 0.069, respectively). The hazard ratio of falls was significantly increased in osteosarcopenia.

3.4. Survival rate and hazard ratio of fractures

The fracture-free survival rates of the 4 groups are shown in Fig. 3. That in the SP + OP + group was 54.5%, significantly lower than that in the SP-OP- group (P = 0.005). The fracture-free survival rates in the SP + OP- and SP-OP + groups were 82.4% and 82.1%, respectively; they were not significantly different compared to that in the SP-OP- group (86.4%).

The hazard ratios of fractures, adjusted by age, sex, and BMI, are shown in Fig. 4. Compared to the SP-OP- group, the hazard ratios were not significantly increased in the SP + OP + group (2.72-fold; P = 0.169), the SP + OP- group (1.27-fold; P = 0.775), and the SP-OP + group (1.09-fold higher; P = 0.890).

3.5. Correlations between disease activity, and body compositions (muscle mass and bone mass) and fall and fracture events

DAS28-ESR at baseline was negatively correlated significantly with muscle mass (r = −0.254, P = 0.026) and bone mass (r = −0.260, P = 0.022) measured after 4 years by a body composition analyzer. However, DAS28-ESR at baseline did not show any correlations with falls (r = −0.117, P = 0.245) and fractures (r = −0.142, P = 0.158) during the 4-year follow-up. SDAI showed the same tendencies with respect to correlations with muscle mass, bone mass, and fall and fracture events.

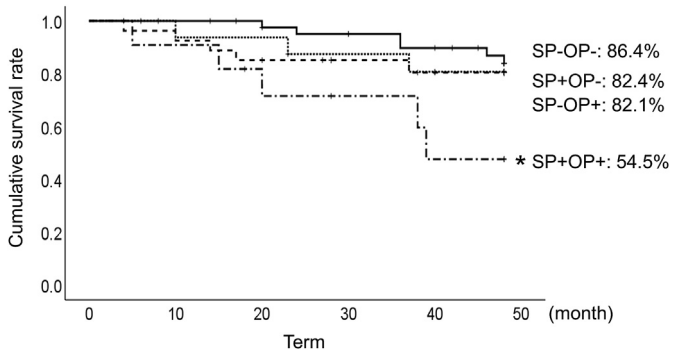

Fig. 3. Fracture-free survival rates of the 4 groups.
There are significant differences among the 4 groups. The rate is significantly lower in the SP + OP + group than in the SP-OP- group (P = 0.005).
SP-OP-: no sarcopenia and no osteoporosis, SP + OP-: only sarcopenia, SP-OP+: only osteoporosis, SP + OP+: both sarcopenia and osteoporosis.
*: Compared among the 4 groups by the log-rank test and with the SP-OP- group using the Bonferroni correction, P < 0.0083.

3.6. Correlations between glucocorticoid and fall and fracture events

The glucocorticoid user at baseline did not show any correlations with falls (r = 0.084, P = 0.408) and fractures (r = −0.103, P = 0.308). The glucocorticoid dosage also did not correlate with falls (r = −0.291, P = 0.158) and fractures (r = −0.231, P = 0.266) by univariate analysis.

4. Discussion

This study examined falls and fractures during 4-year follow-up, and the synergistic effect of osteoporosis and sarcopenia in patients with RA was examined by a longitudinal analysis using data from a prospective, observational study. The fall-free and fracture-free survival rates in osteosarcopenia were slightly lower than those in no sarcopenia and no osteoporosis.

The MMP3 levels of both the SP + OP- and SP + OP + groups were higher than of the no sarcopenia groups at baseline. This result corresponded with our previous report showing that MMP3 was the independent factor associated with sarcopenia in RA [9].

We previously reported that the percentage of RA patients experiencing 1 or more falls during 4-year follow-up was 47% from a prospective cohort study (the TOMORROW study) [19]. In this CHIKARA study, the fall rate was 37%, and this rate was similar to that in the previous study. The fall rate of RA patients was relatively high. Therefore, maintenance of muscle mass and function may be important to prevent falls. The risks of fragility and hip fractures increase about 1.5-fold and 2-fold, relatively, in patients with RA compared to controls [20]. The risk of vertebral fracture was also high in RA [8]. Ochi et al [21] reported that non-vertebral fractures of RA patients did not decrease during 10-year follow-up, despite improvement in disease activity and functional disability in a large cohort. Our data showed that 17% of RA patients had 1 or more fractures during 4-year follow-up, although 38% of all patients were treated for osteoporosis.

Osteoporosis patients (SP-OP+ and SP + OP + group) had already been prescribed osteoporosis drugs at baseline. The details of osteoporosis treatment were: bisphosphonates in 26 cases; active vitamin D in 7 cases; denosumab in 4 cases; and teriparatide

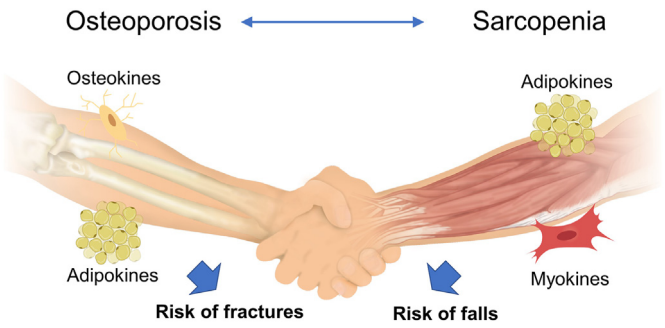

Fig. 5. Interaction of osteoporosis and sarcopenia. Bone and muscle interact with osteokines, myokines, and adipokines. There is an increased risk of falls and fractures due to the synergistic effect of osteoporosis and sarcopenia in patients with RA.

in 2 cases. The treatment period and causal relationship with fractures were not investigated in the present study.

The reasons for fractures other than falls are injuries, fatigue, and unclear. The reason for all fractures was a fall, which included slips, in the present study. The percentages of falls and fractures were 64% and 45% in the osteosarcopenia group. Four of 5 vertebral fractures occurred in the osteosarcopenia group. Osteosarcopenia may be associated with a high risk of fragility fractures.

In community-dwelling older adults, the prevalence of osteosarcopenia is 5–37%, according to a review article. Osteosarcopenia is associated with falls and fractures, with odds ratios of 2.83–3.63 and 3.86–4.38, respectively, compared with no osteosarcopenia [22]. In the present study, there were the same tendencies in patients with RA. The prevalence of osteosarcopenia was 11%, and the hazard ratios of falls and fractures were 3.32 and 2.72, respectively.

The relationship of osteoporosis and sarcopenia is summarized as a schematic diagram (Fig. 5). Osteoporosis is one of the risk factors for fractures, and sarcopenia is one of the risk factors for falls [2,22]. Osteoporosis and sarcopenia interact with each other by osteokines, myokines, and adipokines. Therefore, osteosarcopenia increases both fractures and falls. To prevent falls and fractures, both osteoporosis treatment and sarcopenia prevention may be important.

The disease activity at baseline had negative correlations with muscle mass and bone mass after 4 years. This indicates that patients with high disease activity at baseline had decreased muscle mass and bone mass. However, there were no correlations between disease activity and fall and fracture events. The correlation between body composition, these events and the change in disease activity was not investigated. In the future, we will investigate this relationship.

The glucocorticoid at baseline also did not correlate falls and fractures after 4 years. The relatively low usage rate of glucocorticoid (25%) may be one of the reasons. However, the correlation between falls, fractures, and the change in glucocorticoid during 4 years was not unknown.

The present study has some limitations that must be considered. First, the falls and fractures of drop-out patients (15 cases) were not investigated. Second, the changes in RA disease activity and treatment during the 4-year follow-up may have had an impact on falls and fractures. Third, there was a possibility that osteoporosis treatment reduced the risks of falls and fractures. Forth, the changes of status of sarcopenia and osteoporosis were not evaluated. This change of status may affect the falls and fractures. Fifth, the 25 (OH) vitamin D levels that related the muscle function and falls was not measured, because that was not covered by medical insurance in Japan at the starting of this study.

5. Conclusions

The present study showed that 11% of patients with RA had osteosarcopenia. A total of 37 patients had falls, and 19 patients had fractures during the 4-year follow-up. The hazard ratio of falls was significantly increased in osteosarcopenia by 3.32-fold compared to normal. The fracture-free survival rate of osteosarcopenia was significantly lower than that of normal. These results indicate the increased risk of falls with the synergistic effect of osteoporosis and sarcopenia in patients with RA.

CRediT author statement

Masahiro Tada: Conceptualization, Formal analysis, Data curation, Writing - Original Draft, Writing – Review & Editing.
Yutaro Yamada: Data curation, Writing - Original Draft.
Koji Mandai: Formal analysis, Writing - Original Draft.
Yoshinari Matsumoto: Writing - Original Draft.
Noriaki Hidaka: Writing - Original Draft.

Conflicts of interest

The authors declare no competing interests.

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