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Original article

Long-term changes in lean mass in postmenopausal women and the effects of osteoporosis pharmacotherapy: A 10-year longitudinal study

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ABSTRACT

Objectives: Although sarcopenia is diagnosed using appendicular lean mass (ALM), only a few long-term studies on changes in both ALM and bone mineral density (BMD) have been reported. The purposes of this study are to evaluate the changes in the parameters of lean mass and bone mass over a 10-year interval and to estimate the effects of osteoporosis pharmacotherapy on muscle.

Methods: A total of 175 postmenopausal women were evaluated at baseline and after 10 years for BMD, ALM, fat mass, height, and weight. Subjects were further divided into an osteoporosis treatment group ($n = 60$) and a control group ($n = 67$) according to whether they had received pharmacotherapy for > 5 years. This was followed by propensity score matching for age, height, weight, and body mass index (BMI), and estimated parameters were compared between groups.

Results: Height, weight, ALM, and fat mass decreased significantly over 10 years ($P < 0.05$). However, lean mass index (LMI), derived as the ALM divided by the height squared, increased significantly ($P < 0.001$). BMD increased significantly with osteoporosis treatment ($P < 0.05$), while no significant differences were observed between the osteoporosis treatment and control groups in the changes to ALM or fat mass.

Conclusions: ALM was decreased, while LMI was significantly increased. This contradictory result seems to be affected by age-related height loss. Thus, the effect of height loss needs to be considered when sarcopenia is evaluated longitudinally using LMI.

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1. Introduction

Sarcopenia refers to an excessive loss of muscle mass in older adults that causes functional impairment. This pathologic condition is now one of the most important global health problems. Prevalence of sarcopenia has been estimated to be as high as 29% and 33% in elderly community-dwelling and long-term care populations, respectively [1]. In addition, the overall estimate of the prevalence of sarcopenia was 10% in both men and women, and prevalence was higher among non-Asian individuals than among Asian individuals in both sexes according to a recent systematic review of 35 articles with over 58 000 individuals [2].

Both the European Working Group on Sarcopenia in Older People (EWGSOP) and the Asian Working Group for Sarcopenia (AWGS) have stated that assessment of muscle mass is important in diagnosing sarcopenia [3,4]. AWGS recommends measuring appendicular skeletal muscle mass (ASM) using either dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA) to assess muscle mass for a diagnosis of sarcopenia [3]. AWGS cutoffs for low muscle mass in sarcopenia diagnosis by skeletal muscle mass index (SMI), as calculated using ASM and height, are < 7.0 kg/m^2 in men and < 5.4 kg/m^2 in women by DXA, and < 7.0 kg/m^2 in men and < 5.7 kg/m^2 in women by BIA [3]. However, no long-term longitudinal studies on changes to ASM and SMI in postmenopausal women appear to have been reported.

On the other hand, the major sign of osteoporosis is the fragility fracture, causing functional impairment and increased mortality and placing a very substantial health burden among elderly populations worldwide. Osteoporosis and sarcopenia often co-exist, and the combined condition diagnosed from the presence of both low bone mass and sarcopenia is commonly referred to as osteosarcopenia [5]. A recent systematic review of the literature revealed that osteosarcopenia may occur in 5–37% of community-dwelling elderly persons [6]. Studies have shown that subjects diagnosed with osteosarcopenia experience reduced handgrip strength, increased chair rise time, and higher risks of falls and fractures,

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compared to patients diagnosed with either sarcopenia or osteopenia alone [7–9].

Therefore, we hypothesized that if osteoporosis is improved by osteoporosis pharmacotherapy, the positive effects on bone may also impact muscle; hence, muscle function and volume may be improved. In fact, clinical trials have shown that several osteoporosis drugs also have effects on muscle. For example, native and active forms of vitamin D are well known to be effective on both bone and muscle [10,11]. In addition, a recent trial that administered denosumab, a humanized monoclonal antibody to the receptor activator of nuclear factor-κB ligand, to postmenopausal women with osteosarcopenia [12] found that those treated with denosumab showed increased appendicular lean mass and handgrip strength compared to those who did not receive treatment [12].

With these, the aims of this longitudinal study are to investigate changes in parameters on skeletal muscle and bone among postmenopausal Japanese women at a 10-year interval and to further evaluate the effects of osteoporosis pharmacotherapy on muscles.

2. Methods

2.1. Subjects and study protocol

A total of 175 postmenopausal women with a mean age of 64 years at baseline (range, 42–79 years) who visited our orthopedic clinic consecutively more than 10 years ago, could be followed-up for more than 10 years thereafter, and were able to undergo evaluation of whole and regional body composition by DXA (QDR 4500A; Hologic, Waltham, MA, USA) both at the initial visit and after 10 years were enrolled in this study.

All subjects were either orthopedic patients who had minor symptoms (ie, sprain, contusion, transient joint pain, etc.) at the initial visit and were recommended to undergo examination for osteoporosis due to their postmenopausal status or were examinees in a regional screening program for osteoporosis who were referred to our clinic for confirmation of the diagnosis of osteoporosis. All subjects were informed about the objectives of DXA and consented. None of the subjects had a history of osteoporosis treatment using anti-osteoporosis drugs at baseline. Subjects with a history of bone metabolic disorders other than osteoporosis (ie, osteomalacia, hyperparathyroidism, etc.), corticosteroid use, malignant disease, paralysis, or inability to walk for any reason (ie, myelopathy, paraplegia, severe osteoarthritis, etc.) were excluded.

2.2. Evaluation of body composition and related parameters

Height (cm), weight (kg), body mass index (BMI, kg/m^2), whole and regional body composition, including whole-body bone mineral density (BMD), whole-body bone mass, whole-body fat mass, appendicular lean mass (ALM), and lean mass index (LMI) ALM was calculated using the whole-body composition data obtained using DXA as the sum of lean mass in the arms and legs, assuming that all non-fat and non-bone tissue is skeletal muscle [13,14]. The methods of DXA measurement and validation have been reported elsewhere [15,16]. LMI was derived as the ALM in kilograms divided by the square of the height in meters [13,17]. Sarcopenia was considered present when an LMI is $\geq$ 2 standard deviation (SD) below the mean in young women [13]. The cutoff value of LMI < 5.4 kg/m^2 advocated by AWGS was used in this study for the definition of low muscle mass in sarcopenia [3]. These evaluations were compared at baseline and after 10 years.

Participants were then divided into 4 groups according to age at baseline, namely age 40–49, 40s; age 50–59, 50s; age 60–69, 60s; and age 70–79, 70s.

Furthermore, subjects were divided according to whether they received treatment or not to examine the effects of anti-osteoporotic agents over time especially on muscle. There were 82 patients who had been treated for >5 years during the course (treatment group) and 93 patients who had not been treated (control group). Then propensity score matching was performed such that age, height, weight, and BMI were equal between the groups, and evaluation items were compared between groups (treatment group: n = 60, and control group: n = 67). Anti-osteoporotic agents for the treatment group included bisphosphonate alone in 60 patients, bisphosphonate with activated vitamin D_3 in 12 patients, selective estrogen receptor modulator in 4 patients, and others in 6 patients. The study protocol was approved by the institutional review board of our university (IRB#:1970). Informed consent was obtained from all subjects for use of their dataset for this study. This study was conducted in accordance with the Declaration of Helsinki.

2.3. Definition of osteoporosis

In this study, the use of anti-osteoporosis agents was initiated after the definitive diagnosis of osteoporosis according to the diagnostic criteria proposed by the World Health Organization [18]. To be succinct, osteoporosis was defined as a BMD $\geq$ 2.5 SDs below the young adult mean (T-score $\leq$ −2.5). BMDs were measured through DXA of both the lumbar spine (L2–L4) and total hip, and osteoporosis was diagnosed if either lumbar spine or hip BMD met the criteria.

2.4. Statistical analysis

All data are presented as means and SDs. Statistical analyses were performed using SPSS® software version 24 (IBM Corp., Armonk, NY, USA). Patients for both original groups were pooled, and the 2 groups were constructed using the nearest-neighbor propensity score-based matching. Patients were matched for baseline age, height, weight, and BMI. Comparisons of data between baseline and follow-up were made using the paired *t*-test. Differences in variables between the 2 groups with or without osteoporosis treatment were assessed using an unpaired *t*-test. Values of $P < 0.05$ were considered statistically significant.

3. Results

3.1. Changes in measured variables over 10 years in all participants

From the data of all 175 subjects, height and weight decreased significantly by an average of 3.1 cm and 1.6 kg, respectively, over

Table 1
Changes in variables after 10 years in all participants (n = 175).

Variable	Baseline	Follow-up	P-value
Age, yr	64.0 ± 8.3	74.2 ± 8.2	
Height, cm	153.2 ± 5.9	150.1 ± 6.8	< 0.001
Weight, kg	53.2 ± 7.5	51.6 ± 8.3	< 0.001
BMI, kg/m^2	22.7 ± 3.2	23.0 ± 3.8	0.037
Whole-body BMD, g/cm^2	0.879 ± 0.11	0.903 ± 0.11	0.001
Whole-body bone mass, kg	1.47 ± 0.28	1.46 ± 0.27	0.452
Whole-body fat mass, kg	17.8 ± 4.8	16.3 ± 5.3	< 0.001
ALM, kg	14.2 ± 1.9	14.1 ± 1.9	0.018
LMI, kg/m^2	6.06 ± 0.7	6.26 ± 0.8	< 0.001
Sarcopenia	26/175 (15%)	20/175 (11%)	
T-score of total hip BMD	−1.70 ± 1.1	−2.19 ± 1.06	< 0.001
T-score of lumbar spine BMD	−2.01 ± 1.32	−1.89 ± 1.39	0.089

Values are presented as mean ± standard deviations or number.
BMI, body mass index; BMD, bone mineral density; ALM, appendicular lean mass; LMI, lean mass index.

Table 2
Changes in variables after 10 years for patients in their 40s (n = 9).

Variable	Baseline	Follow-up	P-value
Age, yr	47.5 ± 2.8	57.7 ± 2.9	
Height, cm	156.5 ± 7.7	155.5 ± 8.0	0.032
Weight, kg	50.7 ± 12.4	49.8 ± 11.9	0.642
BMI, kg/m^2	20.5 ± 3.8	20.5 ± 4.0	0.952
Whole-body BMD, g/cm^2	0.995 ± 0.111	0.939 ± 0.105	0.042
Whole-body bone mass, kg	1.72 ± 0.41	1.55 ± 0.36	0.022
Whole-body fat mass, kg	14.7 ± 6.2	13.8 ± 5.6	0.458
ALM, kg	14.6 ± 3.7	14.2 ± 3.0	0.445
LMI, kg/m^2	5.88 ± 1.07	5.84 ± 0.91	0.827
Sarcopenia	4/9 (44%)	3/9 (33%)	
T-score of total hip BMD	−1.12 ± 1.59	−1.90 ± 1.61	0.019
T-score of lumbar spine BMD	−1.04 ± 1.65	−1.75 ± 1.78	0.023

Values are presented as mean ± standard deviation or number.
BMI, body mass index; BMD, bone mineral density; ALM, appendicular lean mass; LMI, lean mass index.

Table 3
Changes in variables after 10 years for patients in their 50s (n = 47).

Variable	Baseline	Follow-up	P-value
Age, yr	55.5 ± 3.0	65.8 ± 3.0	
Height, cm	155.6 ± 5.3	153.3 ± 5.7	< 0.001
Weight, kg	54.3 ± 9.1	54.2 ± 9.1	0.832
BMI, kg/m^2	22.5 ± 3.4	23.1 ± 4.0	0.010
Whole-body BMD, g/cm^2	0.911 ± 0.093	0.891 ± 0.067	0.060
Whole-body bone mass, kg	1.57 ± 0.25	1.49 ± 0.22	< 0.001
Whole-body fat mass, kg	18.1 ± 5.3	17.9 ± 5.7	0.613
ALM, kg	14.4 ± 1.9	14.4 ± 2.1	0.629
LMI, kg/m^2	5.96 ± 0.76	6.15 ± 0.93	0.003
Sarcopenia	10/47 (21%)	7/47 (15%)	
T-score of total hip BMD	−1.47 ± 1.15	−2.07 ± 0.88	< 0.001
T-score of lumbar spine BMD	−1.48 ± 1.30	−1.73 ± 1.29	0.076

Values are presented as mean ± standard deviation or number.
BMI, body mass index; BMD, bone mineral density; ALM, appendicular lean mass; LMI, lean mass index.

the course of 10 years (P < 0.001, Table 1). BMI also increased significantly (P < 0.05). After 10 years, whole-body BMD was significantly increased, while fat mass and ALM were significantly decreased (P < 0.05). On the other hand, no change was identified for bone mass. Furthermore, LMI increased significantly over 10 years (P < 0.001). The prevalence of sarcopenia had slightly declined after 10 years (11%) compared to the baseline (15%). The T-score of total hip BMD significantly decreased, while T-score of lumbar spine BMD did not change.

3.2. Changes in measured variables over 10 years by age group

Data for each age group are listed in Tables 2–5. Height significantly decreased in all age groups (1.1 cm in 40s, 2.3 cm in 50s, 2.9 cm in 60s, and 5.1 cm in 70s; P < 0.05). Weight also significantly decreased in the 60s and 70s (P < 0.001), but not in the 40s and 50s. BMI increased significantly only in the 50s (P = 0.01), with no change in any other age group. Whole-body BMD significantly decreased in the 40s but significantly increased in the 60s and 70s (P < 0.05). Similarly, bone mass significantly decreased in the 40s and 50s, but increased significantly in the 70s (P < 0.05). Fat mass did not show any significant changes in the 40s or 50s, but significantly decreased in the 60s and 70s (P < 0.001). A significant decrease in ALM was found only in the 70s (P = 0.021). LMI significantly increased in all age groups (P < 0.01) except for the 40s. Prevalence of sarcopenia declined in all age groups. The T-score of total hip BMD significantly decreased in all age groups. The T-score of lumbar spine decreased in the 40s (P < 0.05), while increased in the 70s (P < 0.001).

3.3. Effects of osteoporosis pharmacotherapy on measured variables for 10 years

At baseline, patients who underwent osteoporosis treatment with anti-osteoporotic agents were significantly older and showed a lower height, weight, and BMI (Table 6). Followed by the propensity score matching for age, height, weight, and BMI, the 2 groups were compared (Table 7).

After 10 years, height and weight significantly decreased in both groups. BMI increased in the treatment group. Whole-body BMD significantly increased and fat mass decreased in both groups, while no change was found in whole body bone mass. LMI significantly increased in both groups, while no change was found in ALM. The T-score of total hip BMD significantly decreased in both groups, while the T-score of lumbar spine BMD significantly increased only in the treatment group.

Table 4
Changes in variables after 10 years for patients in their 60s (n = 71).

Variable	Baseline	Follow-up	P-value
Age, yr	65.0 ± 2.8	75.3 ± 2.9	
Height, cm	153.2 ± 4.9	150.4 ± 5.3	< 0.001
Weight, kg	53.5 ± 6.4	51.5 ± 6.9	< 0.001
BMI, kg/m^2	22.8 ± 2.9	22.8 ± 3.3	0.990
Whole-body BMD, g/cm^2	0.867 ± 0.117	0.902 ± 0.101	0.002
Whole-body bone mass, kg	1.46 ± 0.26	1.46 ± 0.25	0.819
Whole-body fat mass, kg	18.2 ± 4.3	16.3 ± 4.8	< 0.001
ALM, kg	14.3 ± 1.5	14.1 ± 1.4	0.063
LMI, kg/m^2	6.11 ± 0.6	6.27 ± 0.6	0.003
Sarcopenia	8/71 (11%)	7/71 (10%)	
T-score of total hip BMD	−1.66 ± 1.85	−2.10 ± 1.05	< 0.001
T-score of lumbar spine BMD	−2.17 ± 1.26	−2.01 ± 1.40	0.128

Values are presented as mean ± standard deviation or number.
BMI, body mass index; BMD, bone mineral density; ALM, appendicular lean mass; LMI, lean mass index.

Table 5
Changes in variables after 10 years for patients in their 70s (n = 48).

Variable	Baseline	Follow-up	P-value
Age, yr	73.8 ± 2.7	84.0 ± 2.8	
Height, cm	150.5 ± 6.3	145.4 ± 6.8	< 0.001
Weight, kg	52.1 ± 7.4	49.6 ± 8.1	< 0.001
BMI, kg/m^2	23.0 ± 3.1	23.5 ± 3.7	0.070
Whole-body BMD, g/cm^2	0.842 ± 0.108	0.908 ± 0.141	< 0.001
Whole-body bone mass, kg	1.34 ± 0.26	1.41 ± 0.33	0.014
Whole-body fat mass, kg	17.5 ± 4.6	15.6 ± 5.3	< 0.001
ALM, kg	13.9 ± 1.8	13.6 ± 1.9	0.021
LMI, kg/m^2	6.13 ± 0.7	6.44 ± 0.8	< 0.001
Sarcopenia	4/48 (8%)	2/48 (4%)	
T-score of total hip BMD	−2.09 ± 1.06	−2.49 ± 1.08	< 0.001
T-score of lumbar spine BMD	−2.48 ± 1.13	−1.88 ± 1.43	< 0.001

Values are presented as mean ± standard deviation or number.
BMI, body mass index; BMD, bone mineral density; ALM, appendicular lean mass; LMI, lean mass index.

The increase in BMI was significantly greater in the treatment group than the control group, while no differences were found regarding the changes in height and weight. No significant differences were found regarding changes in whole-body BMD, bone mass, fat mass, ALM, and LMI between groups. Furthermore, the increase in the T-score of lumbar spine BMD was significantly greater in the treatment group than in the control group, and the decrease of the total hip BMD was significantly smaller in the treatment group.

Table 6
Baseline characteristics of all the subjects in the variables with or without treatment of osteoporosis.

Variable	Control (n = 93)	Treatment (n = 82)	P-value (unpaired *t*-test)
Age at baseline, yr	62.1 ± 8.6	66.1 ± 7.4	<0.001
Height, cm	154.2 ± 5.7	152.1 ± 5.9	0.017
Weight, kg	55.2 ± 8.1	50.9 ± 6.0	<0.001
BMI, kg/m^2	23.3 ± 3.5	22.0 ± 3.5	0.010

Values are presented as mean ± standard deviation or number.
BMI, body mass index.

Table 7
Comparison in variables with or without treatment of osteoporosis followed by propensity score matching.

Variable	Control (n = 67)	Treatment (n = 60)	P-value (unpaired *t*-test)
Age at baseline, yr	65.0 ± 7.4	65.0 ± 6.6	0.990
Height, cm			
Baseline	153.1 ± 4.7	153.7 ± 4.8	0.449
Follow-up	150.4 ± 5.4	150.1 ± 6.4	0.804
Change	−2.7 ± 2.4	−3.6 ± 3.2	0.074
P-value (paired *t*-test)	< 0.001	< 0.001	
Weight, kg			
Baseline	52.9 ± 7.0	53.0 ± 4.7	0.932
Follow-up	50.7 ± 7.6	51.7 ± 5.8	0.430
Change	−2.2 ± 4.3	−1.3 ± 4.1	0.251
P-value (paired *t*-test)	< 0.001	0.018	
BMI, kg/m^2			
Baseline	22.6 ± 3.3	22.4 ± 2.2	0.759
Follow-up	22.5 ± 3.7	22.9 ± 3.0	0.381
Change	−0.1 ± 1.7	0.5 ± 2.0	0.04
P-value (paired *t*-test)	0.553	0.035	
Whole-body BMD, g/cm^2			
Baseline	0.887 ± 0.09	0.853 ± 0.128	0.084
Follow-up	0.917 ± 0.106	0.892 ± 0.11	0.295
Change	0.026 ± 0.099	0.039 ± 0.10	0.438
P-value (paired *t*-test)	0.044	0.001	
Bone mass, kg			
Baseline	1.49 ± 0.27	1.42 ± 0.26	0.087
Follow-up	1.47 ± 0.26	1.45 ± 0.27	0.616
Change	−0.02 ± 0.21	0.03 ± 0.20	0.617
P-value (paired *t*-test)	0.428	0.246	
Fat mass, kg			
Baseline	17.6 ± 4.7	17.9 ± 3.17	0.608
Follow-up	15.9 ± 4.9	16.7 ± 4.1	0.366
Change	−1.7 ± 3.2	−1.2 ± 3.1	0.519
P-value (paired *t*-test)	< 0.001	0.003	
ALM, kg			
Baseline	14.1 ± 1.7	14.1 ± 1.4	0.917
Follow-up	13.9 ± 1.7	13.9 ± 1.5	0.816
Change	−0.2 ± 0.9	−0.2 ± 0.9	0.543
P-value (paired *t*-test)	0.300	0.265	
LMI, kg/cm^2			
Baseline	6.03 ± 0.69	5.96 ± 0.62	0.619
Follow-up	6.14 ± 0.76	6.21 ± 0.76	0.611
Change	0.11 ± 0.44	0.25 ± 0.45	0.111
P-value (paired *t*-test)	0.03	< 0.001	
T-score of total hip BMD			
Baseline	−1.55 ± 1.06	−2.04 ± 0.84	0.005
Follow-up	−2.24 ± 1.04	−2.27 ± 0.95	0.879
Change	−0.69 ± 0.62	−0.23 ± 0.50	< 0.001
P-value (paired *t*-test)	< 0.001	0.001	
T-score of lumbar spine BMD			
Baseline	−1.74 ± 1.19	−2.48 ± 0.82	< 0.001
Follow-up	−1.85 ± 1.37	−1.93 ± 1.27	0.726
Change	−0.11 ± 0.81	0.55 ± 0.95	< 0.001
P-value (paired *t*-test)	0.273	< 0.001	

Values are presented as mean ± standard deviation or number.
BMI, body mass index; BMD, bone mineral density; ALM, appendicular lean mass; LMI, lean mass index.

4. Discussion

4.1. Impact of height loss on LMI and sarcopenia diagnosis

ALM as measured by DXA is an important indicator of muscle mass in older adults. In this study, ALM significantly decreased over 10 years, while unexpectedly, LMI significantly increased and the prevalence of sarcopenia as diagnosed using LMI decreased. These trends were seen across all age groups. These contradicting results appeared attributable, at least in part, to the loss of height with the progression of aging. The height of subjects in this study decreased by an average of 3.1 cm over the course of 10 years. Thus, the impact

of age-related height loss needs to be considered when LMI, which is derived by dividing ALM by the square of the height, is used for the evaluation of muscle mass and diagnosis of sarcopenia.

Age-related height loss commonly occurs in the elderly, especially in osteoporotic patients with vertebral fractures and spinal kyphosis. However, arm span is unaffected by height loss and can be a reliable predictor of peak height. Arm span and height are known to remain consistent from the 20s to the 40s [19]. In a recent study that used BIA, we compared the diagnostic accuracy of height-adjusted SMI and arm span-adjusted SMI to diagnosis sarcopenia in a total of 55 women with postmenopausal osteoporosis aged 62–95 years [20]. The prevalence of sarcopenia was found to be higher when using arm span-adjusted SMI (38.2%) than when using height-adjusted SMI (27.3%). These findings have suggested that arm span-adjusted calculation may be more appropriate for the diagnosis of sarcopenia in older adults with height loss, particularly with osteoporotic vertebral fractures and spinal kyphosis. In elderly individuals, height-adjusted SMI may overestimate muscle mass. Our previous study showed that patients with presarcopenia showed a larger difference in arm span height and lower BMD as compared to the normal subjects [20]. Considering the results of the present study, the measurement of the arm span is highly recommended along with the measurement of height for elderly subjects, and an obvious discrepancy between the two are found, arm span-adjusted SMI may be more suitable to reveal the true status of the muscle mass.

In addition, to accurately diagnose sarcopenia, muscle strength and physical performance should also be evaluated along with muscle mass [3,4]. Recently, the Sarcopenia Definition and Outcomes Consortium (SDOC), which was funded by the National Institute on Aging (NIA) and the Foundation for the National Institutes of Health (FNIH), crafted a position statement on the definition of sarcopenia based on a review of the literature [21]. In this statement, a low grip strength and usual gait speed independently predicted falls, mobility limitation, hip fractures, and mortality among community-dwelling elderlies, while lean mass as measured by DXA was not associated with any incident adverse health-related outcomes [21].

4.2. Impact of osteoporosis pharmacotherapy on muscle

Skeletal muscle mass is generally recognized as being correlated with bone mass. As such, we hypothesized that the treatment of osteoporosis with anti-osteoporotic agents may also positively affect the status of the muscle. However, in the present study, an increase in lumbar spine BMD due to anti-osteoporosis agents showed no significant correlation with changes in ALM, ie, history of osteoporosis pharmacotherapy for > 5 years showed no significant positive effects on ALM compared to controls.

Possible mechanisms contributing to the development of osteosarcopenia may involve the interplay of hormonal, nutritional, genetic, and lifestyle factors [5]. Studies have shown that osteoporosis and sarcopenia share multiple factors with aging, such as age-related reductions in the levels of sex steroid hormones [22,23], changes in nutritional status including vitamin D insufficiency [24], and impaired growth hormone and insulin-like growth factor-I signaling and activity [25,26]. Due to these muscle-bone interactions, diminished or improved muscle mass and quality would also theoretically correlate with diminished or improved bone mass and quality.

In fact, significant associations between lean mass and BMD have been previously reported in clinical studies [27–29]. A study of 2400 Japanese women (mean age, 66 years) has also reported that muscle mass, as determined by SMI from DXA, was significantly associated with both osteopenia and osteoporosis [29]. In this cohort, significant and marginal/moderate positive correlations were observed between SMI and lumbar spine/total hip BMDs ($r = 0.197$ and $r = 0.274$, respectively; $P < 0.0001$ each), and the prevalence of sarcopenia, as defined by LMI, was highest in those with osteoporosis, followed by patients with osteopenia, and lowest in those with normal BMD [29]. In addition to muscle mass, another study showed that muscle strength also displayed significant associations with BMD, especially in a site-specific manner [27]. In a study of postmenopausal women, quadriceps strength showed a great association with hip BMD, but not with lumbar spine BMD [27].

The present study used a retrospective cohort design, with changes in ALM and LMI over 10 years as the primary endpoints, and the effect of osteoporosis drugs on muscle as the secondary endpoint. Subjects who had been treated for >5 years (as more than half of 10 years) were assigned as the osteoporosis treatment group for convenience. Therefore, we did not compare subjects who had been treated with anti-osteoporosis agents for the complete 10 years with those who had not been treated for osteoporosis at all for 10 years. Since observing osteoporosis patients without treatment as untreated controls is not ethically feasible, we settled on the present study design. However, the grouping we decided on in this study may have unintentionally influenced the effects of anti-osteoporosis agents on muscles. Some untreated controls may have received inadequate treatment for less than 5 years, but any details regarding this were not detected from the interviews or chart-based retrospective surveys in this study.

A notable finding was observed that whole-body BMD increased in the control group, while the total bone mass did not change. On the other hand, lumbar spine and hip BMD decreased in this group, indicating the natural course in those patients without treatment for osteoporosis. BMD is derived as the bone mass in grams divided by the square of the area of bone in centimeters. Then, if the height decreased and bone mass unchanged, the calculated whole-body BMD would increase. Therefore, the increase in whole-body BMD may be due to the effect of height loss as well as the unexpected increase in LMI.

4.3. Study limitations

A key strength of the present study was its novelty in simultaneously observing changes in muscle mass and BMD over a long period of 10 years in postmenopausal women. In addition, the study was able to examine the effects of osteoporosis drugs on muscles. However, several study limitations should be mentioned. First, in addition to the grouping issue stated above, we were unable to analyze the effects of each anti-osteoporosis agents owing to the study subjects using a variety of drugs; some drugs were used for many patients and others were not. Therefore, this study analyzed all osteoporosis drugs together. Second, since the number of cases varied by age group, detailed comparisons between age groups could not be performed. Third, vertebral fractures might have contributed to age-related height loss, but no spine X-ray data were available in this study. Fourth, due to the retrospective nature, this study failed to follow the subjects who dropped out due to other diseases or other reasons during the observation of 10 years. Further high-quality longitudinal prospective studies that address these limitations will soon be necessary.

5. Conclusions

This study investigated changes in lean mass and BMD over a 10-year interval in 175 postmenopausal Japanese women and examined the effects of anti-osteoporotic agents on lean mass. ALM decreased significantly over time; however, LMI unexpectedly

increased significantly, and the prevalence of sarcopenia decreased over the 10 years. These contradictory results were affected by height loss with aging. ALM and fat mass did not change regardless of the use of anti-osteoporosis agent.

CRediT authorship contribution statement

Naohisa Miyakoshi: Conceptualization, Methodology, Validation, Writing – review & editing. **Michio Hongo:** Investigation, Data curation, Formal analysis, Writing – review & editing. **Yoichi Shimada:** Supervision, Project administration.

Conflicts of interest

The authors declare no competing interests.

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