frequency and exercise intensity (metabolic equivalents [MET]) of their physical activity habits during leisure time over the preceding 12 months.[18] The means per day for leisure-time physical activity (metabolic equivalents; MET × h/day) were calculated. Nutritional intake was assessed with a 3-day diet record.[19] Foods were weighed separately on a scale before cooking, or portion sizes were estimated. Participants used a disposable camera to take photographs of meals before and after eating. Registered dieticians used the photographs to complete missing data, and telephoned participants to resolve any discrepancies or to obtain further information when necessary. The average over the 3 days for 119 nutrient intake periods was calculated. The means per day for total energy intake (kcal/day), total protein intake (g/day) and vitamin D intake (μg/day) were calculated from the 3-day dietary record.

Statistical analysis

Statistical testing was carried out using the Statistical Analysis System release 9.3 (SAS Institute, Cary, NC, USA). A probability level less than 0.05 was considered significant. The results are shown as the means ± standard deviation (SD). Cochran–Mantel–Haenszel statistics were used to examine the trends for the decade of age, and the androgen levels and the prevalence of sarcopenia. The trends for the androgen levels and the prevalence of sarcopenia were also examined using Cochran–Mantel–Haenszel statistics.

Multiple logistic regression models were fit to determine the associations of TT, FT and DHEA-S with sarcopenia while controlling for baseline age group, BMI, leisure-time physical activity, serum C-reactive protein level, nutritional intakes (total energy, total protein, vitamin D), medical history (heart disease, diabetes, osteoporosis, rheumatic arthritis), current smoking, and menopause as possible confounders.

TT was modeled by tertile at the baseline examination (low group, <15.0 ng/dL; middle group, 15.0 to <24.8 ng/dL; high group, ≥24.8 ng/dL). FT was modeled as three groups at the baseline examination: the low-level group (<0.7 pg/mL), the middle-level group (0.7 to <1.2 pg/mL) and the high-level group (≥1.2 pg/mL). An FT of 0.7 pg/mL was the detection limit of the RIA in the FT measurements, according to the manufacturer's information. Approximately 40% of participants in the present study were classified in the low group (Table 2). An FT of 1.2 pg/mL was the median of the participants who were not classified in the low group. DHEA-S was also modeled by tertile at the baseline examination (low group, <706 ng/mL; middle group, 706 to <1160 ng/mL; high group, ≥1160 ng/mL).

Analyses were carried out with an unadjusted crude model and several adjusted models, controlling for different combinations of confounding variables: the baseline decade of age group and BMI were taken as moderator variables in model 1; and the baseline decade of age group, BMI, leisure-time physical activity, nutritional intakes, medical histories, menopause and smoking habit were considered moderator values in model 2.

Results

Table 1 presents the basic characteristics of the 430 participants at baseline. The mean follow-up duration of all participants was 8.3 ± 0.3 years. The mean age of all participants was 55.3 ± 9.8 years. The number of menopausal participants was 269 (62.6%).

Table 2 shows the percentages for each androgen group stratified by decade of age. There were no significant trends for the TT and FT groups by age decade. The percentage of participants in low group for DHEA-S increased with age (P trend < 0.0001).

Figure 1 presents the prevalence of sarcopenia at the time of follow-up by age decade at baseline. Participants with sarcopenia included 24 (16.4%) of 146 in the 40s age group, nine (6.7%) of 134 in the 50s age group, seven (7.3%) of 96 in the 60s age group and six (11.1%) of 54 in the 70s age group. There was no significant correlation between aging and the prevalence of sarcopenia.

Figure 2 presents the prevalence of sarcopenia in the testosterone and DHEA-S groups. In the TT group, the numbers of participants with sarcopenia in the low group (n = 143), middle group (n = 142) and high group (n = 145) were 17 (11.9%), 19 (13.4%), and 10 (6.9%), respectively. There were no significant relationships between TT level and the prevalence of sarcopenia. In the FT group, the numbers of participants with sarcopenia in the low group (n = 180), middle group (n = 127) and high group (n = 123) were 30 (16.7%), 11 (8.7%), and five (4.1%), respectively. Increases in the serum FT level reduced the prevalence of participants with sarcopenia (P trend = 0.0004). In the DHEA-S group, the numbers of participants with sarcopenia in the low group (n = 140), middle group (n = 138) and high group (n = 152) were 16 (11.4%), 14 (10.1%), and 16 (10.5%), respectively. There was no significant relationship between the DHEA-S level and the prevalence of sarcopenia.

The results of multiple logistic regression analyses for risk of sarcopenia by differences in androgen levels are shown in Table 3. The FT levels were significantly associated with sarcopenia. In the crude model, the odds ratio of sarcopenia for the Low-FT group compared with the high-FT group was 4.72 (95% confidence interval [CI] 1.78–12.54, P = 0.0008). In model 1, the odds ratio of sarcopenia for the low-FT group compared with the high-FT group was 3.15 (95% CI 1.13–8.82, P = 0.0105). In model 2, the odds ratio of sarcopenia for

Table 1 Characteristics of participants at baseline by follow-up status

Characteristics	Participants (n = 430)
Mean follow up (years)	8.3 ± 0.3
Age (years)	55.3 ± 9.8
Body height (cm)	153.0 ± 5.3
Bodyweight (kg)	54.6 ± 7.5
Body mass index (kg/m^2)	23.3 ± 3.0
Percentage of body fat	31.3 ± 4.8
Appendicular skeletal muscle mass (kg)	14.7 ± 1.7
Skeletal muscle index (kg/m^2)	6.3 ± 0.6
Total energy intake (kcal/day)	1958.1 ± 307.0
Total protein intake (g/day)	76.1 ± 15.1
Vitamin D intake (μg/day)	9.0 ± 6.4
Leisure-time physical activity (MET × h/day)	1.5 ± 1.9
C-reactive protein (ng/mL)	821.5 ± 2207.8
Total testosterone (ng/dL)	21.1 ± 9.9
Free testosterone (pg/mL)†	1.0 ± 0.5
Dehydroepiandrosterone-sulfate (ng/mL)	996.0 ± 515.8
Estradiol (pg/mL)	40.4 ± 59.9
Menopause (n)	269 (62.6%)
Smokers (n)	31 (7.2%)
Heart disease (n)	32 (7.4%)
Diabetes (n)	13 (3.0%)
Osteoporosis (n)	29 (6.7%)
Rheumatoid arthritis (n)	36 (8.4%)

Data are reported as means ± SD or n (%). †The free testosterone level included 0.7 pg/mL, which was the lower limit of detection by radioimmunoassay, and was calculated.

the low-FT group compared with the high-FT group was 3.59 (95% CI 1.25–10.34, P = 0.0070). A significant negative trend (crude model, P-trend = 0.0008; model 1, P-trend = 0.0105; model 2, P-trend = 0.0007) in the odds ratios of sarcopenia was found with increasing serum FT level in each model. Sarcopenia showed no significant relationships with TT and DHEA-S.

Discussion

This is the first study to show a longitudinal association between serum FT level and sarcopenia over 8 years of follow up in Japanese women. It is well known that testosterone stimulates protein synthesis and inhibits protein degradation in muscle cells.[20,21] However, it has remained unclear whether endogenous androgens are associated with sarcopenia in women, because few cross-sectional studies have been published about the associations between the decreases of lean mass and the circulating androgen levels in women.[9,11] In the present study, significant associations between muscle loss and FT, but not TT, which does not have bioavailability, remained after adjustment for age, medical history, menopause, smoking habit, nutritional intake and physical activity. The present result is in line with previous studies that reported an association between low FT and low lean mass in postmenopausal Caucasian, African-American, and Dutch women.[9,11] Circulating FT levels might be a good marker for the loss of muscle mass in middle-aged and elderly Japanese women.

The previous studies reported that muscle mass is associated with the serum testosterone level in men.[5–8] In middle-aged and elderly men, the circulating testosterone level declined linearly with age.[22] In contrast, the serum testosterone level in women decreased by approximately 50%, from the 20s through the 40s, whereas it did not change significantly in the menopause transition stage.[23,24] Monitoring of the serum testosterone level before the menopausal transition could be effective to prevent sarcopenia in women.

In the present cohort, participants in the low-FT group (<0.7 pg/mL) had an approximately threefold risk of muscle loss compared with those in the high-FT group (≥1.2 pg/mL). Improvement in circulating FT levels with appropriate therapies might reduce the risk of sarcopenia in women. Testosterone replacement therapies for elderly men improved muscle mass.[23,24]

Table 2 Androgen secretion capacities at baseline, stratified by age decade

		Age group				Total (n = 430)
		40s (n = 146)	50s (n = 134)	60s (n = 96)	70s (n = 54)	
TT group, n (%)	Low (<15.0 ng/dL)	46 (31.5%)	45 (33.6%)	37 (38.5%)	15 (27.8%)	143 (33.3%)
	Middle (15.0 to <24.8 ng/dL)	50 (34.3%)	40 (29.9%)	31 (32.3%)	21 (38.9%)	142 (33.0%)
	High (≥24.8 ng/dL)	50 (34.2%)	49 (36.5%)	28 (29.2%)	18 (33.3%)	145 (33.7%)
		P-trend = 0.6758				
FT group, n (%)	Low (<0.7 pg/mL)	59 (40.4%)	61 (45.5%)	37 (38.5%)	23 (42.6%)	180 (41.9%)
	Middle (0.7 to <1.2 pg/mL)	41 (28.1%)	37 (27.6%)	30 (31.3%)	19 (35.2%)	127 (29.5%)
	High (≥1.2 pg/mL)	46 (31.5%)	36 (26.9%)	29 (30.2%)	12 (22.2%)	123 (28.6%)
		P-trend = 0.5969				
DHEA-S group, n (%)	Low (<706 ng/mL)	21 (14.4%)	45 (33.6%)	45 (46.9%)	29 (53.7%)	140 (32.6%)
	Middle (706 to <1160 ng/mL)	46 (31.5%)	43 (32.1%)	34 (35.4%)	15 (27.8%)	138 (32.1%)
	High (≥1160 ng/mL)	79 (54.1%)	46 (34.3%)	17 (17.7%)	10 (18.5%)	152 (35.3%)
		P-trend < 0.0001				

The trend P-values were obtained using the Cochran–Mantel–Haenszel test. DHEA-S, dehydroepiandrosterone-sulphate; FT, free testosterone; TT, total testosterone.

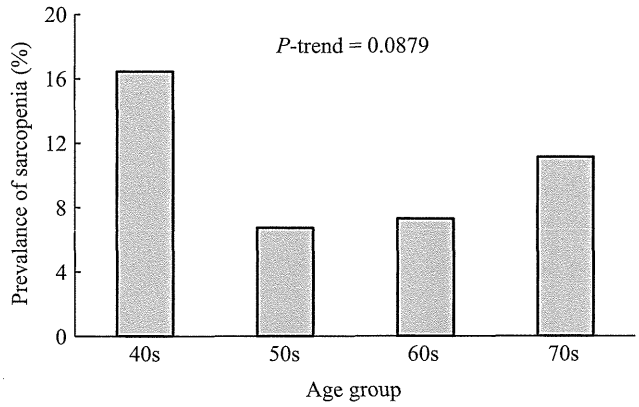

Figure 1 Prevalence of sarcopenia at the follow-up examinations by age group at baseline. The trend P-values were obtained using the Cochran–Mantel–Haenszel test.

Testosterone replacement therapy for 3 weeks also raised the rate of muscular protein synthesis in premenopausal women.[25] However, testosterone replacement therapy might induce cardiovascular events.[26] Bioavailable testosterone showed a U-shaped association with incident coronary heart disease in menopausal women.[27] In addition, a high FT level is associated with the incidence of type 2 diabetes in menopausal women.[28] Further studies that examine an appropriate range of the serum testosterone level in women are required.

Interestingly, although previous reports suggested that serum DHEA-S levels are associated with longevity and frailty, the serum DHEA-S level was not associated with muscle loss in the present study.[12–14] The effects of DHEA on the preservation of muscle mass during aging have not been determined. DHEA-S was positively associated with lean body mass measured by DXA in 244 community-dwelling, African-American women aged 49–65 years.[10] In contrast, DHEA replacement for 2 years raised serum DHEA-S concentrations in 27 elderly women, whereas the thigh-muscle area measured by computed tomography and fat-free mass measured by DXA did not change significantly.[29] Appendicular muscle mass did not correlate with age in Japanese women aged 40–88 years.[30] In the present study, the prevalence of sarcopenia was not changed by age group (Fig. 1). The circulating testosterone level in women does not change significantly during the menopausal transition.[24,31,32] The bioactivity of DHEA is weaker than that of testosterone, and the serum DHEA levels in women decrease with aging.[24] The effect of DHEA on muscle protein metabolism in women might be more limited than that of testosterone. Furthermore, a low serum DHEA-S level is associated with impairment in instrumental activities of daily living or physical function.[10,33] DHEA might be essential to neural

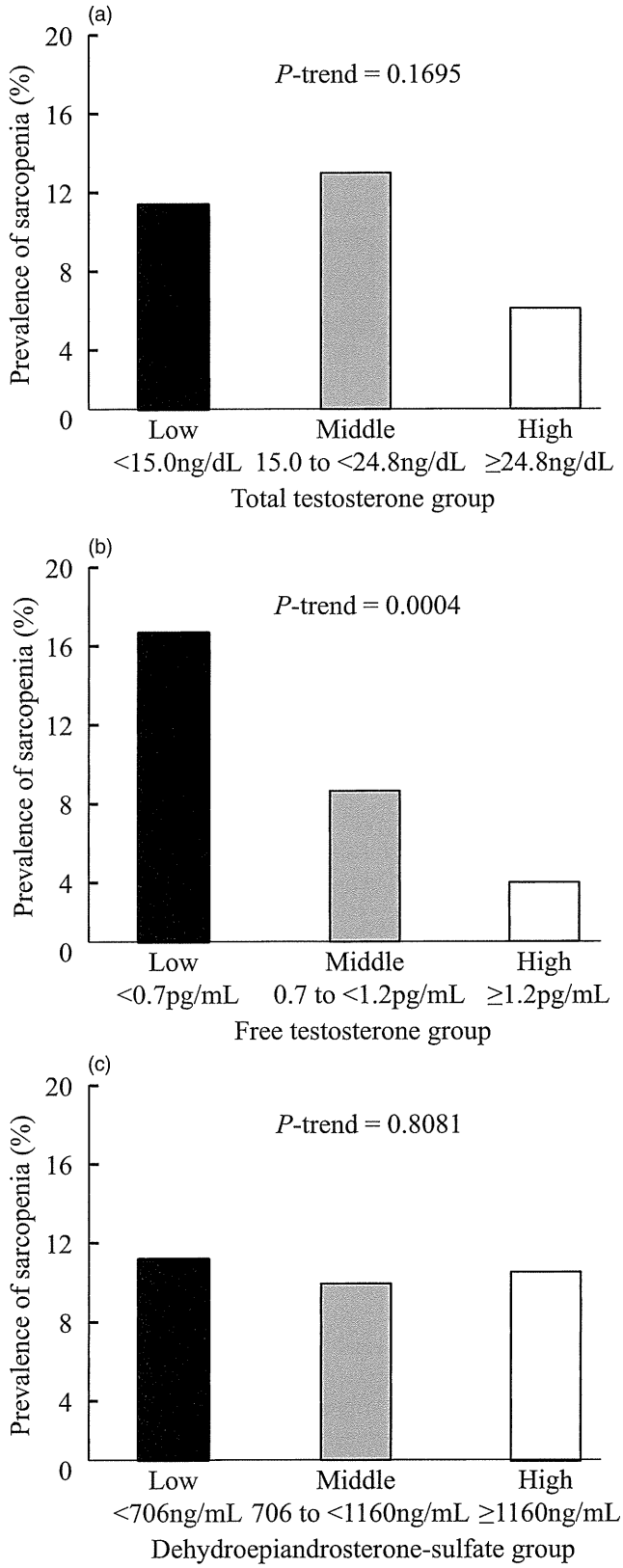

Figure 2 Prevalence of sarcopenia at the follow-up examinations by (a) total testosterone, (b) free testosterone and (c) dehydroepiandrosterone-sulphate at baseline. The trend *P*-values were obtained using the Cochran–Mantel–Haenszel test.

functions, including motor control, rather than preservation of muscle mass.

A limitation of the present study was that FT was measured by RIA. RIA-based FT measurements offer only limited precision and specificity in the low-level range of women compared with that based on liquid chromatography-tandem mass spectrometry methods.[34] However, RIA is generally used for measurement of FT in Japan, because RIA is easier to carry out than the liquid chromatography-tandem mass spectrometry methods. In the present study, the FT levels of approximately 40% of participants were below the lower limit for detection. Further studies that measure FT by liquid chromatography-tandem mass spectrometry methods are required to determine the role of FT in preserving muscle mass in women with lower FT levels.

Another limitation of the present study was the anthropometry analyses involving only DXA. We could not measure muscle strength or physical performance, which are both considered components of sarcopenia in modern definitions.[4,35] Assessment of muscle strength and physical performance is also important in evaluating activities of daily living.[4] Further analyses that muscle strength and physical performance were used for the dependent variables are required to determine the association between testosterone and activities of daily living.

In summary, using the longitudinal design of the NILS-LSA cohort, the association between loss of muscle mass and endogenous androgen levels was evaluated in community-dwelling, middle-aged and elderly Japanese women with an 8-year follow-up duration. The present data confirm that a low FT level is a significant predictor of the risk for loss of appendicular muscle. The findings in the present study could be beneficial for developing methods to prevent sarcopenia in Japanese women.

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Disclosure statement

The authors have no conflicts of interest to disclose.

Table 3 Longitudinal relationships between the androgen groups and sarcopenia

		n	Odds ratio (95% confidence intervals)		
			Crude model	Model 1	Model 2
TT group	Low (<15.0 ng/dL)	143	1.82 (0.80–4.13)	1.26 (0.52–3.02)	1.32 (0.53–3.27)
	Middle (15.0 to <24.8 ng/dL)	142	2.09 (0.93–4.66)	2.07 (0.87–4.90)	2.14 (0.89–5.16)
	High (≥24.8 ng/dL)	145	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	P trend		0.4816	0.7045	0.7816
FT group	Low (<0.7 pg/mL)	180	4.72 (1.78–12.54)	3.15 (1.13–8.82)	3.59 (1.25–10.34)
	Middle (0.7 to <1.2 pg/mL)	127	2.24 (0.75–6.64)	1.54 (0.49–4.84)	1.67 (0.52–5.36)
	High (≥1.2 pg/mL)	123	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	P trend		0.0008	0.0105	0.007
DHEA-S group	Low (<706 ng/mL)	140	1.10 (0.53–2.29)	1.34 (0.58–3.11)	1.43 (0.60–3.40)
	Middle (706 to <1160 ng/mL)	138	0.96 (0.45–2.05)	0.99 (0.43–2.26)	0.96 (0.41–2.22)
	High (≥1160 ng/mL)	152	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	P trend		0.7309	0.4231	0.3317

Moderator variable: Crude model: none; Model 1: baseline age group, body mass index; Model 2: age group, leisure-time physical activity, nutritional intake (total energy, total protein, vitamin D), C-reactive protein, medical histories (heart disease, diabetes, osteoporosis, rheumatoid arthritis), smoking habit, and menopause at baseline. DHEA-S, dehydroepiandrosterone-sulphate; FT, free testosterone; TT, total testosterone.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Sex- and age-related differences in mid-thigh composition and muscle quality determined by computed tomography in middle-aged and elderly Japanese

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Aim: Sex- and age-related differences in mid-thigh composition and muscle quality remain unclear. The present study aimed to clarify these differences using computed tomography in middle-aged and elderly Japanese.

Methods: A total of 2310 participants (age 40–89 years), who were randomly selected from the local residents, underwent computed tomography examination of the right mid-thigh. Thigh circumference and cross-sectional areas of the thigh, muscle, quadriceps, non-quadriceps, fat, and bone were measured. Knee extension strength and muscle quality index (knee extension strength/quadriceps cross-sectional area) were also assessed. Sex- and age-related differences in these indices were analyzed.

Results: The thigh cross-sectional area in men and women decreased by 0.6% and 0.5%/year, respectively, because of a decrease in muscle cross-sectional area (men 75.2%, women 40.6%), fat cross-sectional area (men 24.4%, women 59.6%) and bone cross-sectional area (men 0.5%, women −0.2%). Muscle cross-sectional area in men and women decreased by 0.6% and 0.4%/year, respectively, because of a decrease in quadriceps cross-sectional area (men 65.6%, women 81.6%) and non-quadriceps cross-sectional area (men 34.4%, women 18.4%). Muscle quality in men and women decreased by 0.4% and 0.3%/year, respectively.

Conclusion: Thigh cross-sectional area decreased with age mainly because of a decrease in muscle cross-sectional area in men and fat cross-sectional area in women. The rate of decrease in muscle cross-sectional area was 1.5-fold higher in men than in women. Muscle cross-sectional area decreased with age mainly because of a decrease in quadriceps cross-sectional area, especially in women. Decrease in muscle quality with age was similar in both sexes. **Geriatr Gerontol Int 2015; 15: 700–706.**

Keywords: aging, computed tomography, mid-thigh composition, muscle mass, muscle quality.

Introduction

In the rapidly aging Japanese population, frailty secondary to aging has become a concern, as it often requires extensive nursing care. Loss of muscle mass and strength are considered to be the main causes of aging-related frailty; therefore, implementation of measures to prevent this loss is considered necessary. The term "sarcopenia" was first proposed by Rosenberg in 1989, and is defined as a loss of muscle mass and strength.[1] Baumgartner *et al.* proposed that sarcopenia be defined as appendicular skeletal muscle (kg)/height (m^2) of less than two standard deviations below the mean of a young reference group; the reference values used for the diagnosis of sarcopenia have been 7.26 kg/m^2 in men and 5.45 kg/m^2 in women.[2] The definition of sarcopenia was changed by the European Working Group on Sarcopenia in Older People in 2010 to "the presence of low muscle mass and low muscle function (strength or

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performance)".[3] Muscle mass evaluation is necessary to make a diagnosis of sarcopenia based on the European Working Group on Sarcopenia in Older People criteria.[3] Computed tomography (CT),[4–8] magnetic resonance imaging (MRI),[9–11] dual energy X-ray absorptiometry (DXA)[2,12] and bioimpedance analysis (BIA)[13] have been used for evaluating muscle mass.[3] Clinically, DXA and BIA have been used most commonly, as they are convenient and economical; however, CT and MRI are considered precise imaging systems that could separate fat from other soft tissues and individual muscle parts, and are therefore the gold standard methods for estimating muscle mass in research.[3] Previously, studies have evaluated muscle mass based on mid-thigh CT;[4–8] however, these studies involved either small sample sizes[7] or a narrow age range.[8] Therefore, sex- and age-related differences in mid-thigh composition, including muscle mass determined by CT, remained unclear.

Furthermore, there was no research available on the evaluation of total thigh composition including thigh circumference, and thigh, muscle, quadriceps (Qc), non-Qc, fat and bone cross-sectional areas (CSA) determined by mid-thigh CT. Sex- and age-related differences in these indices also remained unclear.

Muscle strength decreases with age,[14–16] and it decreases to a greater extent than muscle mass.[8] Some studies have evaluated muscle strength/muscle mass as an index of muscle quality, but the sample sizes were small and these studies did not distinguish between the sexes.[8,17] The aim of the present study was to clarify sex- and age-related differences in mid-thigh composition and muscle quality using CT in a middle-aged and elderly Japanese population.

Methods

Participants

Study participants were selected from the seventh wave examination (July 2010 to July 2012) participants of the National Institute for Longevity Sciences – Longitudinal Study of Aging (NILS-LSA). NILS-LSA is a longitudinal, dynamic cohort study that includes medical, physiological, nutritional, and psychological examinations. Age- and sex-matched participants equal to the number of dropout participants were selected randomly, except for those who were aged over 79 years. Male and female participants aged 40 years were also newly recruited every year. Details of the NILS-LSA have been previously reported.[18] A total of 2330 men and women aged 40–89 years were randomly chosen from the residents registered with the local governments of Obu City and Higashiura Town, Aichi, Japan. Of the 2330 participants of the seventh wave examination, 1174 men and 1136 women underwent mid-thigh CT examination and were included in the present study; 20 participants rejected CT examination and were excluded from this study. Of these 2310 participants, muscle knee extension strength (KES) and KES/Qc CSA analysis were successfully measured in 1091 men and 978 women; the measurement was stopped if the participant complained of pain or refused to participate. The NILS-LSA was approved by the ethics committee of the National Center for Geriatrics and Gerontology, and written informed consent was obtained from all participants.

Measurement of mid-thigh CSA

Right mid-thigh CSA was measured by CT (X-Vision; Toshiba, Tokyo, Japan and SOMATOM Sensation 64; Siemens, Munich, Germany) with the patient in a supine position at the midpoint from the inguinal crease to the proximal pole of the patella.[5,6] Single-slice CT image was obtained with a minimal slice width of 10 mm for X-Vision and 5 mm for SOMATOM Sensation 64. Thigh CSA, thigh circumference, muscle CSA, Qc CSA, non-Qc CSA, fat CSA and bone CSA were analyzed using Quick Grain version 5.2 software (Inotech, Hiroshima, Japan). The differences in CT voxels between air and skin, fat and muscle, and muscle and bone were checked by an orthopedic surgeon before calculation of thigh CSA, thigh circumference, muscle CSA and bone CSA by automatic tracing of the margins. Subcutaneous and intermuscular fat CSA and bone CSA were removed when muscle CSA was measured (Fig. 1). Qc CSA was measured by manual tracing

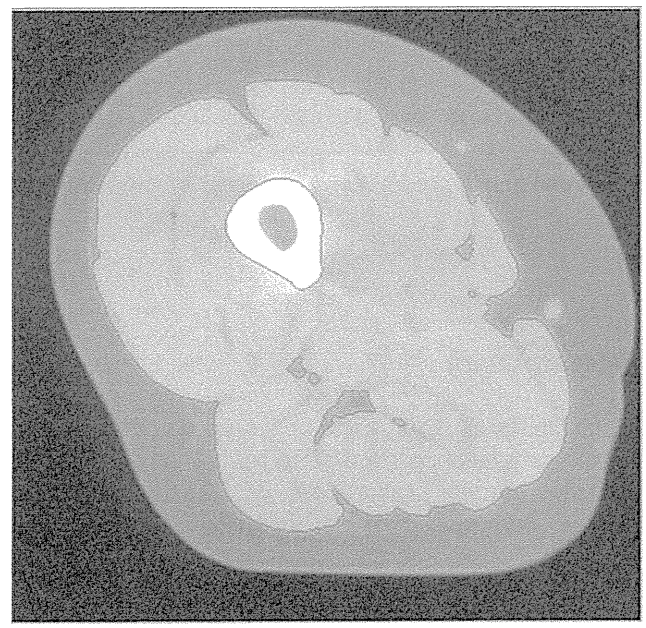

Figure 1 Mid-thigh cross-sectional area. Muscle cross-sectional area is shown. Subcutaneous and intermuscular fat cross-sectional area, and bone cross-sectional area have been removed.

Table 1 Characteristics of the subjects

	Men (n = 1174)	Women (n = 1136)	P-value
Age (years)	61.4 ± 12.6	61.3 ± 12.8	0.8219
40s, n (%)	268 (22.8%)	273 (24.0%)	
50s, n (%)	262 (22.3%)	258 (22.7%)	
60s, n (%)	284 (24.2%)	261 (23.0%)	0.933
70s, n (%)	262 (22.3%)	242 (21.3%)	
80s, n (%)	98 (8.3%)	102 (9.0%)	
Body height (cm)	166.6 ± 6.6	153.0 ± 6.2	<0.0001
Bodyweight (kg)	64.3 ± 9.6	52.2 ± 8.9	<0.0001
Body mass index (kg/m^2)	23.1 ± 2.8	22.3 ± 3.4	<0.0001
Stroke, n (%)	54 (4.6%)	38 (3.4%)	0.1232
Heart disease, n (%)	69 (5.9%)	46 (4.1%)	0.0434
Diabetes, n (%)	99 (8.4%)	66 (5.8%)	0.0144
Hypertension, n (%)	389 (33.1%)	313 (27.6%)	0.0035
Hyperlipidemia, n (%)	235 (20.0%)	257 (22.6%)	0.1261
Smoker, n (%)	231 (19.7%)	44 (3.9%)	<0.0001
Vitamin D administration, n (%)	8 (0.7%)	40 (3.5%)	<0.0001

The values are expressed as number (% of total men or women) of samples and mean ± standard deviation. P-values were obtained using the t-test for continuous data and the χ^2-test for categorical data.

of the Qc muscle margin. Non-Qc CSA was calculated as muscle CSA minus Qc CSA. Fat CSA was calculated as thigh CSA minus muscle and bone CSA.

Measurement of KES

Isometric KES was measured using T.K.K.1281a (Takei Scientific Instruments, Niigata, Japan). The participants were seated on a chair with their hip and knee joints flexed to 90°, and isometric KES was measured three times. The highest measured value was used for the evaluation.

Evaluation of "muscle quality"

KES/Qc CSA was calculated as an index of muscle quality.[17]

Other parameters

Body height and weight were assessed for all participants. Body mass index (kg/m^2) was calculated by weight/height squared. Medical history, including smoking status and vitamin D administration, was obtained with the use of questionnaires.

Statistical analysis

Statistical testing was carried out using the Statistical Analysis System release 9.3 (SAS Institute, Cary, NC, USA). Differences in continuous variables between men and women were tested by Student's t-test, and associations of class variables between men and women were tested by the χ^2-test. Trends in sex- and age-related differences in each CSA, KES and KES/Qc CSA were tested using a general linear model. For an analysis of differences between age groups, the participants were divided into 10 groups based on sex and age (40s: 40–49 years, 50s: 50–59 years, 60s: 60–69 years, 70s: 70–79 years and 80s: 80–89 years for each sex). Differences among age groups were tested using Tukey–Kramer test for each sex. $P < 0.05$ was considered statistically significant.

Results

Characteristics of the participants

Table 1 shows the characteristics of the participants. The proportion of male and female participants was similar in all age groups (P = 0.9330). The number of participants in the 80s group was approximately half of that in the other groups. Body height, bodyweight and body mass index were significantly higher in men than in women ($P < 0.0001$). The prevalence of heart disease, diabetes, hypertension and current smoking was higher in men than in women (P = 0.0434, 0.0144, 0.0035 and <0.0001, respectively). The prevalence of vitamin D administration was higher in women (3.5%) than in men (0.7%).

Sex- and age-related differences in mid-thigh CSA

Table 2 shows sex- and age-related differences in mid-thigh CSA. The estimated thigh CSA value was 223.4 cm^2 (74.4% muscle CSA, 22.6% fat CSA and 3.0% bone CSA) in 40-year-old men, and 208.9 cm^2 (56.1% muscle CSA, 41.4% fat CSA and 2.4% bone CSA) in 40-year-old women. Thigh CSA decreased with age at a rate of 0.6% per year in men and 0.5% per year in women. The regression line slope of thigh CSA was greater in men than in women ($P = 0.0319$). Thigh CSA decreased as a result of a decrease in muscle CSA (men 75.2%, women 40.6%), fat CSA (men 24.4%, women 59.6%) and bone CSA (men 0.5%, women –0.2%). Thigh CSA decreased mainly as a result of muscle CSA in men and fat CSA in women.

The estimated value of thigh CSA was 161.2 cm^2 (74.1% muscle CSA, 21.9% fat CSA and 4.0% bone CSA) in 89-year-old men, and 158.3 cm^2 (61.1% muscle CSA, 35.5% fat CSA and 3.1% bone CSA) in 89-year-old women. Mid-thigh composition did not differ by age in men. However, in women, the muscle CSA proportion in thigh CSA increased with age, and fat CSA proportion decreased with age.

The estimated value of muscle CSA was 166.2 cm^2 (48.9% Qc CSA, 51.1% non-Qc CSA) in 40-year-old men, and 117.2 cm^2 (47.7% Qc CSA, 52.4% non-Qc CSA) in 40-year-old women. Muscle CSA decreased with age at a rate of 0.6% per year in men and 0.4% per year in women. The regression line slope of muscle CSA was greater in men than in women ($P < 0.0001$). Muscle CSA decreased as a result of Qc CSA (men 65.6%, women 81.6%) and non-Qc CSA (men 34.4%, women 18.4%). The rate of decrease in muscle CSA was 1.5-fold higher in men than in women, and muscle CSA decreased with age mainly because of Qc CSA, especially in women.

Sex- and age-related differences of KES and KES/Qc CSA

Table 3 shows sex- and age-related differences of KES and KES/Qc CSA. KES/Qc CSA was greater in men than women in each age group except the 80s age group. The estimated value of KES/Qc CSA was 7.071 N/cm^2 in 40-year-old men and 6.217 N/cm^2 in 40-year-old women. KES/Qc CSA decreased with age at a rate of 0.4% per year in men and 0.3% per year in women. There was no statistical difference in the slope of KES/Qc CSA between men and women ($P = 0.0935$). Muscle quality was greater in men than in women in each age group except the 80s age group, and showed a similar decrease in both sexes.

Table 2 Mid-thigh cross sectional area

	Men						Women					
	40s ($n = 268$)	50s ($n = 262$)	60s ($n = 284$)	70s ($n = 262$)	80s ($n = 98$)	*P* for trend*	40s ($n = 273$)	50s ($n = 258$)	60s ($n = 261$)	70s ($n = 242$)	80s ($n = 102$)	*P* for trend*
Thigh CSA (cm^2)	216.8 ± 1.9	207.3 ± 1.9	191.2 ± 1.8	180.3 ± 1.8	167.7 ± 3.1	<0.0001	199.9 ± 2.2	198.2 ± 2.2	184.3 ± 2.2	175.9 ± 2.3	156.6 ± 3.5	<0.0001
	40s > 50s > 60s > 70s > 80s†						40s, 50s > 60s, 70s > 80s†					
Thigh circumference (cm)	55.4 ± 0.3	54.3 ± 0.3	52.2 ± 0.2	50.8 ± 0.3	49.2 ± 0.4	<0.0001	53.0 ± 0.3	52.9 ± 0.3	51.1 ± 0.3	50.1 ± 0.3	47.5 ± 0.5	<0.0001
	40s > 50s > 60s > 70s > 80s†						40s, 50s > 60s, 70s > 80s†					
Muscle CSA (cm^2)	158.8 ± 1.3	155.6 ± 1.3	144.6 ± 1.2	133.3 ± 1.3	121.0 ± 2.1	<0.0001	113.1 ± 1.1	113.2 ± 1.1	107.7 ± 1.1	104.4 ± 1.1	93.8 ± 1.7	<0.0001
	40s, 50s > 60s > 70s > 80s†						40s, 50s > 60s, 70s > 80s†					
Quadriceps CSA (cm^2)	77.4 ± 0.6	73.5 ± 0.6	66.3 ± 0.6	59.7 ± 0.6	53.4 ± 1.0	<0.0001	53.4 ± 0.5	51.6 ± 0.5	47.5 ± 0.5	45.0 ± 0.5	38.9 ± 0.8	<0.0001
	40s >50s >60s >70s >80s†						40s, 50s >60s >70s >80s†					
Non-quadriceps CSA (cm^2)	81.4 ± 0.8	82.2 ± 0.8	78.3 ± 0.8	73.6 ± 0.8	67.6 ± 1.3	<0.0001	59.6 ± 0.7	61.6 ± 0.7	60.2 ± 0.7	59.4 ± 0.8	54.9 ± 1.2	<0.0001
	40s, 50s > 60s > 70s > 80s†						40s, 50s, 60s, 70s > 80s†					
Fat CSA (cm^2)	51.2 ± 1.1	45.0 ± 1.1	40.0 ± 1.0	40.4 ± 1.1	40.1 ± 1.8	<0.0001	81.5 ± 1.6	79.7 ± 1.7	71.2 ± 1.7	66.1 ± 1.7	57.4 ± 2.7	<0.0001
	40s > 50s > 60s, 70s, 80s†						40s, 50s > 60s, 70s > 80s†					
Bone CSA (cm^2)	6.74 ± 0.05	6.67 ± 0.05	6.60 ± 0.05	6.54 ± 0.05	6.58 ± 0.08	0.02	5.31 ± 0.04	5.22 ± 0.04	5.29 ± 0.04	5.35 ± 0.04	5.42 ± 0.07	0.0428
	40s > 70s†						Not significant for any age groups†					

*Trend tests examine the main effects of age in each cross-sectional area (CSA). †Tukey–Kramer tests examine the significant difference among each age group. >Indicates the significant difference between the age groups, with *P*-value less than 0.05. The values are expressed as means ± standard error. Non-quadriceps CSA was calculated by muscle CSA minus quadriceps CSA. Age groups: 40s, 40–49 years age group; 50s, 50–59 years age group; 60s, 60–69 years age group; 70s, 70–79 years age group; 80s, 80–89 years age group.

Table 3 Knee extension strength and knee extension strength/quadriceps cross-sectional area

	Men						Women					
	40s (n = 263)	50s (n = 254)	60s (n = 270)	70s (n = 227)	80s (n = 77)	P for trend*	40s (n = 268)	50s (n = 243)	60s (n = 227)	70s (n = 188)	80s (n = 52)	P for trend*
Knee extension strength (n)	520.7 ± 5.9	499.2 ± 5.9	443.3 ± 5.9	370.7 ± 6.9	301.1 ± 10.8	<0.0001	322.6 ± 3.9	307.9 ± 4.9	280.5 ± 4.9	254.0 ± 4.9	208.9 ± 9.8	<0.0001
	40s, 50s > 60s > 70s > 80s†						40s, 50s > 60s > 70s > 80s†					
Knee extension strength/quadriceps CSA (n/cm^2)	6.76 ± 0.08	6.85 ± 0.08	6.68 ± 0.08	6.17 ± 0.08	5.56 ± 0.14	<0.0001	6.09 ± 0.08	5.99 ± 0.08	5.87 ± 0.08	5.61 ± 0.09	5.16 ± 0.18	<0.0001
	40s, 50s, 60s > 70s > 80s†						40s, 50s, 60s > 80s., 40s, 50s > 70s†					

*Trend tests examine main effects of age. †Tukey–Kramer tests examine the significant difference among each age group. >Indicates the significant difference between the age groups, with P-value less than 0.05. The values are expressed as mean ± standard error. Age groups: 40s, 40–49 years age group; 50s, 50–59 years age group; 60s, 60–69 years age group; 70s, 70–79 years age group; 80s, 80–89 years age group. CSA, cross-sectional area.

Discussion

In the present study, thigh CSA decreased with age mainly as a result of a decrease in muscle CSA in men, and fat CSA in women. In men, mid-thigh composition did not differ by age. However, in women, the muscle CSA proportion in thigh CSA increased with age, but the fat CSA proportion decreased with age. The loss of muscle CSA and fat CSA between men and women differed in the present study.

The association of muscle mass and sex hormones has been investigated in some studies. In men, free testosterone decreased with age, and loss of free testosterone was associated with loss of skeletal muscle mass.[19,20] Testosterone supplementation for 6 months increased muscle mass and decreased fat mass.[21] These results suggest that testosterone increases muscle mass, and support the age-related differences in muscle CSA in the present study.

In women, muscle CSA and fat CSA were almost unchanged from the 40s to 50s, but decreased from the 50s to 80s in the present study. In previous studies, a positive relationship was seen between muscle mass and estrogen levels.[22] Muscle mass correlated significantly with plasma estrone and estradiol levels in women.[23] However, the opposite; that is, estrogen not being associated with muscle mass in women, has also been reported.[24] The hypothesis that loss of estrogen could decrease muscle mass is still unproven. Regarding the relationship between estrogen and muscle mass, skeletal mass has estrogen beta-receptors on the cell and nuclear membranes.[25] Therefore, a direct potential mechanistic link could exist between low estrogen levels and a decrease in protein synthesis.[26] We believe that estrogen is associated with muscle mass, which would explain the decrease in muscle CSA in women during menopause.

Regarding fat mass, few studies reported the association of fat mass and sex hormones. Sipila *et al.* reported that estradiol and noretisterone acetate intake for 12 months significantly decreased the relative proportion of fat in quadriceps in menopausal women.[27] This suggests that estrogen might decrease fat mass. In the present study, however, the fat mass decreased gradually from the 50s to 80s. Further studies are required to clarify the effect of estrogen on fat mass.

In the present study, muscle CSA decreased 0.6% per year in men and 0.4% per year in women, and decreased mainly as a result of Qc CSA, especially in women. Qc CSA was negatively correlated with age in both sexes, but non-Qc CSA was negatively correlated with age only in men.[5] The reduction in muscle CSA could be explained by loss in the anterior compartment of the thigh, whereas no changes were observed in the posterior compartment (with no distinction of sex).[28] These reports showed that the decrease of mid-thigh muscle

CSA with age might be mainly as a result of a decrease in Qc CSA, especially in women, and supported the results of the present study. Qc muscle decrease resulted in loss of KES,[28] and loss of muscle mass and KES were associated with increasing risk of mobility loss in older men and women.[29] Thus, Qc muscle mass preservation might be of utmost importance in the maintenance of lower leg muscle mass and function.

Bone CSA decreased 0.09% per year in men and increased 0.04% per year in women. Bone CSA was almost unchanged with age in both sexes. In a previous report, androgen increased periosteal apposition, whereas estrogen inhibited periosteal apposition during puberty.[30] Androgen and estrogen decrease with age; therefore, periosteal apposition, which increases bone CSA, might decrease in men and increase in women of advanced age. The present results supported this consideration. In contrast, we also considered the fact that in the femur, cortical thickness is the greatest in the middle of the bone, which could have influenced bone CSA to be almost unchanged with age.

In the present study, muscle quality was greater in men than in women in each age group except the 80s, and it showed a similar decrease with age in both sexes. In previous studies, muscle strength/CSA did not change with age in subjects aged 23–57 years, but it decreased with age in those aged 65–80 years.[17] Muscle strength/CSA showed a significant decrease with increasing age in men, but not in women.[10] These reports support the fact that muscle quality decreases with age; however, these studies were different from the present study in some respects, possibly because of a difference in the number of participants involved. We believe that the similarity in the decrease of muscle quality showed that muscle fat infiltration[31] or denervation of muscle fibers[32] occur similarly in both sexes.

We reported that the muscle volume of all limbs determined by DXA decreased with age in men, but not in women.[33] In the present study, muscle mass determined by mid-thigh CT decreased in both sexes. We believe that the difference was as a result of measurement methods used. Roth *et al.* reported muscle volume (determined by MRI), rather than muscle CSA, and recommended studying muscle mass responses to strength training.[9] In the present study, CSA was measured by single slice CT at mid-thigh, and therefore, the image might not have shown the entire thigh muscle mass and fat mass.

This study had some limitations. Skeletal muscle attenuation has been associated with skeletal muscle lipid content.[34] Loss of leg muscle torque in older adults was greater than the muscle CSA loss, and aging was associated with an increase in intermuscular fat, which suggested a decrease in muscle quality.[31] It is important to evaluate muscle lipid content for an assessment of muscle quality; however, this study did not evaluate skeletal muscle lipid content. In addition, a longitudinal study is more accurate than a cross-sectional study for an evaluation of age-related changes, but the present study was not a longitudinal study. Young subjects were not included in this study, and therefore, we have not shown the differences across all ages and the mean values for young adults could not be calculated. If we could include young subjects, we could show not only the aging process, but also the growing process. The Asian Working Group for Sarcopenia reported the cut-off values for handgrip strength and the usual gait speed.[35] It is important to show the relationship between handgrip strength and usual gait speed and muscle CSA, knee extension strength, and muscle quality, and to determine the cut-off value for muscle CSA. However, we require more analytical data, and need to consider other aspects to show the relationship and to determine the cut-off value for muscle CSA. We would like to report the details of this concern in another manuscript.

In the present study, we showed the sex- and age-related differences in mid-thigh CSA using CT. Furthermore, compared with other studies of its kind, our study had the largest sample size and the widest age-range in the Asian population. These results will be useful for future studies, such as those carried out on aging and physiology.

In summary, thigh CSA decreased with age mainly as a result of a decrease in muscle CSA in men and fat CSA in women. Mid-thigh composition in men did not change with age. However, in women, the muscle CSA proportion in thigh CSA increased with age and fat CSA proportion decreased. The rate of decrease in muscle CSA was 1.5-fold higher in men than in women. Muscle CSA decreased with age mainly as a result of a decrease in Qc CSA, especially in women. Muscle quality was greater in men than in women in each group except the 80s, and it showed a similar decrease with age in both sexes. These results thus suggest quadriceps muscle training would be the most important to keep leg muscle mass and function, which lead to preventing sarcopenia.

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Disclosure statement

The authors declare no conflict of interest.

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Original article

Effect of alendronate on muscle mass: Investigation in patients with osteoporosis

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Abstract

Objectives: Many osteoporosis drugs reliably increase bone mass in the elderly; if these drugs also had a positive effect on muscle, their benefit would be even greater. We examined the effect of alendronate monotherapy on muscle mass in patients with osteoporosis.
Methods: In this retrospective cohort, case-control study, patients from an osteoporosis database were divided into 2 groups: alendronate-treated patients (group A; n = 199) and a control group receiving no drug treatment (group C; n = 233). Appendicular skeletal muscle mass (ASM) and skeletal muscle mass index (SMI) measured by dual-energy X-ray absorptiometry were assessed at approximately 1 year. The change in muscle mass was compared between the groups.
Results: At baseline, group A included more women and had lower height, weight, bone mineral content, and muscle mass than group C. A comparison of changes after 1 year—adjusted for age, sex, observation period, body mass index and initial values—revealed that the muscle mass in group A showed increases by 0.137 kg/m^2 in SMI, 514 g in ASM, and 319 g in lower limb muscle mass (LLM). Group C showed no changes in muscle mass. A significant difference in the amount of change in ASM and LLM was found between the groups after adjustment: 2.5 times and 4.4 times higher, respectively, in groups A and C. However, the difference in SMI disappeared after adjustment.
Conclusions: This is the first study to show that alendronate may have a positive effect not only on bone, but on muscle as well.

Keywords: Alendronate; Drug treatment; Muscle mass; Osteoporosis; Sarcopenia

1. Introduction

Muscle decline with age is a well-known cause of decreased walking ability and is a major factor in restricted activities of daily living in the elderly. Sarcopenia, defined as a syndrome that causes physical disability because of decreased muscle mass and strength, leads to reduced quality of life and death [1,2]. The international agreement by the European Working Group on Sarcopenia in Older People states that sarcopenia should be diagnosed using walking ability, muscle strength, and muscle mass, and that judgments on the need for intervention can be made from walking ability and muscle mass levels [3]. The most basic underlying criterion for diagnosis is muscle mass, however [3,4].

Despite the importance placed on muscle mass, reports on drugs that have an effect on muscle mass are limited to testosterone [5–7], angiotensin-converting enzyme inhibitors [8], statins [9,10], and a few others [11]. Moreover, most of these drugs have problems in terms of effect and safety reliability, and there are no drugs that can be used regularly in

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clinical practice [11]. Many osteoporosis drugs reliably increase bone mass and contribute to reducing the risk of fracture in the elderly [12]. If these osteoporosis drugs were also to have a positive effect on muscle mass, their benefit would be even greater and would be of more value to patients. Vitamin D preparations may increase both bone and muscle mass [13,14], but a consistent assessment of their efficacy on muscle mass has not been reported [11]. To our knowledge, the effect of bisphosphonates has not been investigated; therefore, we examined the effect of alendronate monotherapy on muscle mass in osteoporosis patients.

2. Materials and methods

The study design was a case-control study with a retrospective cohort. In our hospital, dual-energy X-ray absorptiometry (DXA) bone density measurements of the lumbar spine, hip, and total body have been done since the hospital acquired a DXA machine (DXP-NT; GE Medical Systems Lunar, Madison, WI, USA). Using total body bone measurements in addition to total bone mineral content (BMC) and total fat mass (FM), the appendicular skeletal muscle mass (ASM), which correlates most closely with muscle mass, and skeletal muscle mass index (SMI), a corrected value for physique based on the individual's height, can be calculated [15]. Lower limb muscle mass (LLM) can also be obtained.

Between April 1992 and May 2011, body composition was measured by DXA in 5999 patients and osteoporosis drugs were prescribed to 33,734 patients, of whom 1283 were diagnosed with osteoporosis and included in a database. After excluding those patients who used other drugs, those who received combination therapy, and those assessed by DXA for less than 6 months or more than 1.5 years, 199 patients treated with alendronate monotherapy (35 mg or 5 mg, both doses approved by the Ministry of Health, Labour and Welfare in Japan) for 1 year and evaluated by DXA (group A) and a control group of 233 patients who received no drug therapy for 1 year also observed with DXA only (group C) were selected (Fig. 1). These 2 groups are the subjects of this analysis.

Sarcopenia was judged based on SMI only because full data on walking ability and muscle strength were not available. Patients with levels below the Japanese criteria (men 6.87 kg/m^2, women 5.46 kg/m^2) [16] were diagnosed as having sarcopenia and patients with levels above those values were not. The main outcome variables were skeletal muscle mass (ASM, SMI and LLM).

Statistical analysis was determined using SAS, version 9.2 (SAS Institute Inc.); $p < 0.05$ indicated significance. The amount of change in response variables was compared between the 2 groups. Differences in the amount of change after 1 year were determined using a general linear model with correction for age, sex, observation period, body mass index (BMI), and initial value for each item. Secondary analyses included the correlation between the amount of change in muscle and other body components after 1 year and the difference in the amount of change in muscle in patients receiving 35 mg and 5 mg of alendronate.

This study was approved by the Institutional Review Board. Its approval number is No. 687-2.

3. Results

A comparison of patient baseline characteristics showed no difference in mean age (72.4 years) between the groups. Group

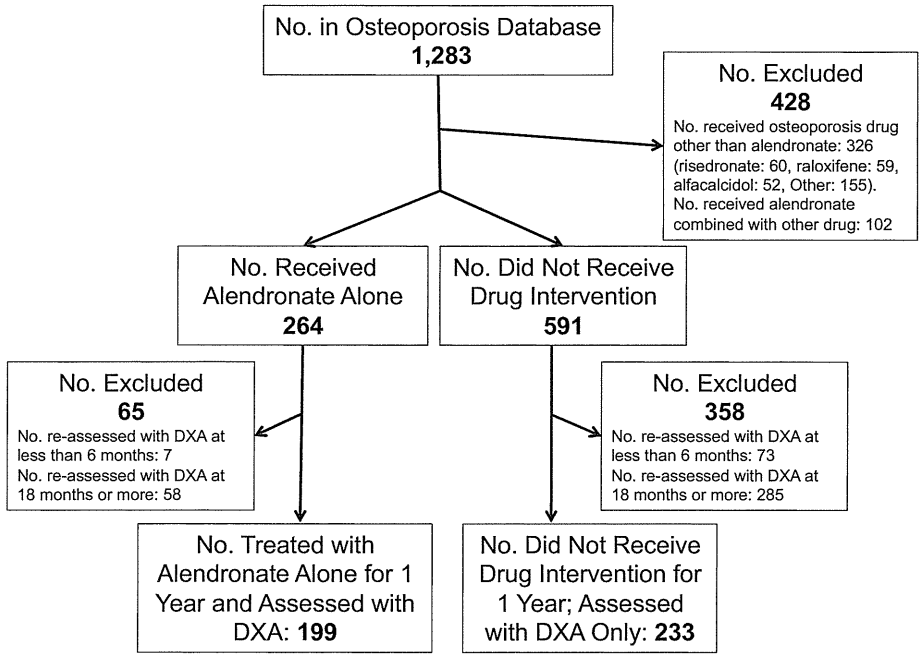

Fig. 1. Flow diagram of subject selection. Patients receiving alendronate monotherapy and those who were untreated and in whom changes in muscle-related items could be measured with total body DXA for 1 year were extracted from an osteoporosis database. DXA: dual-energy X-ray absorptiometry; no.: number.

A had a larger proportion of women than did group C, and a lower height and body weight. However, there was no difference in BMI. In addition, group A patients had lower SMI, ASM, and LLM than group C—in addition to less change in muscle mass and lower BMC—but there was no difference in FM. At baseline, 77 patients (38.7%) in group A had a diagnosis of sarcopenia versus 75 (32.2%) in group C. The between-group difference in these percentages was not significant (Table 1). Moreover, the mean and standard deviation (SD) of the observation period was 357.5 (SD 80.2) days in group A, and 359.9 (SD 89.5) days in group C, with no significant difference between the groups.

A comparison of changes without adjustments after 1 year showed no significant changes in muscle-related SMI, ASM, and LLM in group A. However, among other body composition measures, FM increased significantly, but there was no significant change in BMC. In group C, there were significant decreases in SMI, ASM, and LLM. On the other hand, FM increased and BMC decrease significantly. Moreover, there were significantly different amounts of change in SMI, ASM, and LLM between the groups (Table 2).

Because there was a difference in the amount of muscle mass between the groups at baseline, the amount of change at 1 year was compared, with adjustments for age, sex, observation period, BMI, and the initial value of each item. As a result, the amount of change at 1 year in group A increased significantly: by 0.137 kg/m^2 in SMI, 514 g in ASM, and 319 g in LLM. FM also increased significantly, but there was no change in BMC. In group C, FM increased, but there were no significant changes in other items. The difference in the amounts of change in ASM and LLM between the groups was significant even after the adjustments were made. The increases in ASM and LLM were 2.5 times and 4.4 times higher, respectively, in group A than in group C. However, the differences in SMI disappeared after the adjustments were made (Table 2).

A comparison of the correlation of changes in muscle mass and other body composition items between the groups during the year showed that in group A the amounts of change in SMI and ASM were not associated with BMC ($r = 0.105$, $p = 0.142$ and $r = 0.120$, $p = 0.092$, respectively), whereas there was a weak negative correlation with FM ($r = 0.105$, $p = 0.142$ and $r = 0.120$, $p = 0.092$, respectively). In group C, the amounts of change in SMI and ASM showed weak positive correlations with BMC ($r = 0.197$, $p = 0.003$ and $r = 0.249$, $p = 0.000$, respectively) and very weak negative correlations with FM ($r = -164$, $p = 0.012$ and $r = -0.151$, $p = 0.021$, respectively).

The alendronate doses used in group A were 35 mg once per week in 91 patients, 5 mg daily in 102 patients, and both in 5 patients. The change in SMI was 0.087 (SD 0.591) kg/m^2 in patients receiving 35 mg and 0.000 (SD 0.518) kg/m^2 in patients receiving 5 mg, showing no statistically significant difference between the 2. Similarly, the change in ASM was 243 (SD 1353) g in patients receiving 35 mg and −5 (SD 1160) g in patients receiving 5 mg, which also is not significantly different.

4. Discussion

This is the first report to suggest that alendronate monotherapy may help to maintain muscle mass. Muscle and bone support independence in the elderly, but decrease with age. As a result, it is not uncommon for older people to have sarcopenia and osteoporosis [17,18]. Hip fractures from falls are considered one of the worst effects of these conditions [19,20]. Alendronate is a well-known osteoporosis drug for which there is abundant evidence of decreased risk of hip fracture [21,22]—a result of its action in increasing bone mass—but its clinical effect on muscle has remained unknown. A recent case cohort study by Park et al. showed increased grip strength with combination alendronate and calcitriol, but no change in muscle mass [23]. In our retrospective case-control study, ASM increased 2.5-fold in patients receiving alendronate compared with the controls even after adjusting for initial muscle mass. The increase in LLM was a remarkable 4.4-fold. Calcitriol, which Park et al. used in combination with alendronate [23], and other forms of vitamin D have played a role in increasing bone mass. In addition, vitamin D receptors in striated muscle may respond to increases in muscle strength

Table 1
Comparison of baseline characteristics in the 2 groups.

		Alendronate (N = 199)	Control (N = 233)	Difference[a]
Baseline characteristics	Age, mean (SD), y	72.4 (10.5)	72.4 (11.9)	ns
	Female, no. (%)	182 (91.5)	189 (81.1)	P = 0.0021
	Height, mean (SD), cm	149.3 (7.7)	151.4 (9.1)	P = 0.011
	Body weight, mean (SD), kg	47.4 (8.4)	50.1 (11.2)	P = 0.005
	BMI, mean (SD), kg/m^2	21.2 (3.2)	21.7 (3.8)	ns
	SMI, mean (SD), kg/m^2	5.702 (0.757)	6.091 (0.954)	P < 0.0001
	ASM, mean (SD), g	12,720 (1976)	14,073 (3085)	P < 0.0001
	LLM, mean (SD), g	9694 (1503)	10,704 (2299)	P < 0.0001
	FM, mean (SD), g	13,119 (5918)	13,161 (7875)	ns
	BMC, mean (SD), g	1486 (321)	1649 (497)	P < 0.0001
	Sarcopenia, no. (%)	77 (38.7)	75 (32.2)	ns

ASM: appendicular skeletal muscle mass; BMC: total bone mineral content; BMI: body mass index; FM: total fat mass; LLM: lower limb muscle mass; no., number; SD: standard deviation; SMI: skeletal muscle mass index; ns: not significant.

[a] Between-group comparison by t-test or chi-squared test.

Table 2
Comparison of amount of change in muscle, bone, and fat in the 2 groups after 1 year with no adjustments, and with adjustments for age, sex, observation period, BMI, and the initial value of each item.

		Alendronate (N = 199) Difference compared with baseline[a]	Control (N = 233) Difference compared with baseline[a]	Difference between-group[b]
Amount of change after 1 year with no adjustments	Difference in SMI, mean (SD), kg/m^2	0.045 (0.039) ns[a]	−0.102 (0.045) p = 0.0258[a]	p = 0.0166[b]
	Difference in ASM, mean (SD), g	121 (88) ns[a]	−280 (97) p = 0.0043[a]	p = 0.0027[b]
	Difference in LLM, mean (SD), g	63 (73) ns[a]	−237 (69) p = 0.0007[a]	p = 0.0029[b]
	Difference in FM, mean (SD), g	572 (182) p = 0.0019[a]	346 (164) p = 0.036[a]	ns[b]
	Difference in BMC, mean (SD), g	3 (6) ns[a]	−25 (8) p = 0.003[a]	p = 0.0071[b]
Amount of change after 1 year with adjustments	Difference in SMI, mean (SD), kg/m^2	0.137 (0.763)* p = 0.0118[a]	0.050 (0.734) ns[a]	ns[b]
	Difference in ASM, mean (SD), g	514 (1751) p < 0.0001[a]	208 (1797) ns[a]	p = 0.0206[b]
	Difference in LLM, mean (SD), g	319 (1319) p = 0.0007[a]	72 (1334) ns[a]	p = 0.0143[b]
	Difference in FM, mean (SD), g	934 (3141) p < 0.0001[a]	557 (2941) p = 0.004[a]	ns[b]
	Difference in BMC, mean (SD), g	11 (144) ns[a]	−16 (129) ns[a]	p = 0.0096[b]

ASM: appendicular skeletal muscle mass; BMC: total bone mineral content; FM: total fat mass; LLM: lower limb muscle mass; SD: standard deviation; SMI: skeletal muscle mass index; ns: not significant.
[a] Difference compared with baseline by paired t-test.
[b] Between-group comparison by t-test.

and muscle mass [14,24,25]. Moreover, because Park et al.'s study lacked a control comparison, the level of alendronate's contribution in their results is difficult to judge. In our study, although the effect on muscle strength and performance could not be investigated, it is suggested here for the first time that even alendronate alone may produce clinical improvements in muscle mass.

Following are hypotheses for the mechanism by which muscle mass may improve with alendronate. First is a direct action: It is possible that alendronate causes a proliferation of muscle cells or activates muscle metabolism via a direct pharmacological action on as yet unknown muscle stem cells or myocytes. With regard to alendronate's direct effect of on myoblasts, we found in a recent investigation that "alendronate did not affect the morphology, gene expression, or survival of terminally differentiated human myotubes, whereas it prevented proliferation and differentiation of undifferentiated human myogenic cells. It is impossible to exclude the putative secondary effects of [alendronate] that ameliorate muscle function." [26] However, alendronate's contribution to muscle improvement remains unknown. If alendronate does not bind strongly to bone mineral [27], but rather that alendronate in the blood is related to the increased muscle mass in this study, daily formulations that elevate blood levels with a high frequency would be assumed to have a larger effect on muscle mass than once-weekly formulations. However, this result was ruled out because there was no difference between the 2.

Second is the indirect action hypothesis. Alendronate acts in relation to bone metabolism, based on the well-understood suppression of osteoclasts [27]; from this, a secondary muscle improvement may be derived (e.g., when alendronate reduces bone resorption, serum calcium levels fall and intact parathyroid hormones rise). In addition, serum 1,25-dihydroxyvitamin D levels similarly transiently increase from 4 weeks to 24 weeks [28] with alfacalcidol administration and the previously mentioned increase in muscle mass resulting from vitamin D would occur [13,14]. Moreover, alendronate is reported to raise bone strength and lower fracture risk, while also reducing pain, improving activities of daily living [29] and raising quality of life [30]. Improvement in activities of daily living may be linked to improved muscle mass through increased movement. In this investigation, however, although the amounts of change in muscle and bone were positively correlated in group C, this significant relation was lost in group A, a result that does not directly agree with the second hypothesis.

The first limitation of this study is that the research design was not a prospective randomized controlled trial but a retrospective case-control study using an osteoporosis database. Even though all subjects were patients with osteoporosis, group C, which was observed for 1 year without treatment, had milder disease than group A. In addition, at baseline, group C had a naturally higher bone mass than group A. Group C also had higher values for items related to muscle. To minimize the effects of these differences, analysis with correction of the initial values was undertaken for each item. The amount of change in ASM was significant. The second limitation is that, because the analysis was conducted in this way, SMI's

significance did not persist. This may also be affected by multiple inputs of adjusted items, including the square of height. Third, muscle strength, walking speed, and other performance items in the latest diagnostic criteria for sarcopenia were not evaluated; therefore, it remains unknown whether alendronate affects these items. Moreover, vitamin D and substances that are possible muscle markers were not measured; therefore, the range of the analysis was limited to changes in body composition. Consequently, the suggestions obtained in this study will need to be confirmed in a randomized controlled trial in which these issues are resolved. In addition, muscle and bone mass could be affected by several factors, such as physical activity, pain, and the underlying diseases. However, we could not obtain such information from our database, and therefore, this is also limitation of the current study.

In conclusion, our retrospective case-control study showed that ASM increased 2.5-fold with alendronate compared with the controls, even after adjusting for initial muscle mass. The increase in LLM was a remarkable 4.4-fold. This is the first study to show the possibility that alendronate monotherapy has a positive effect not only on bone but also on muscle.

Conflict of interest

No potential conflicts of interest were disclosed.

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《特集》

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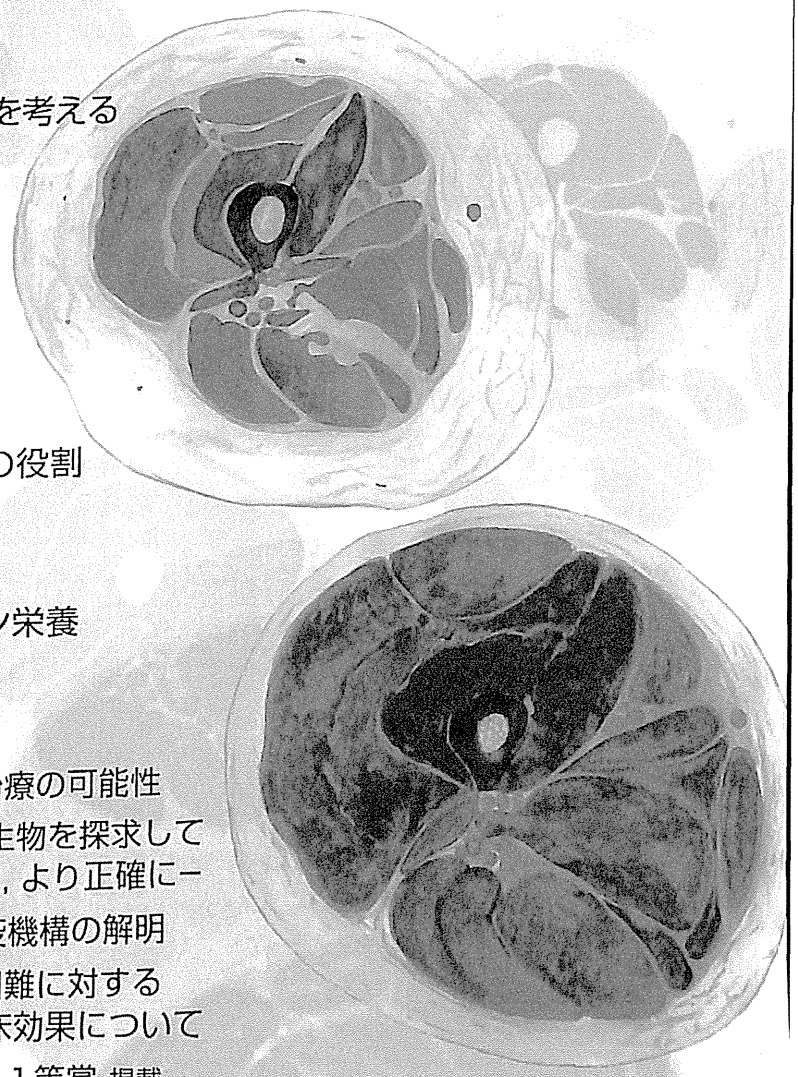
サルコペニアへの介入

サルコペニアとビタミンD



◆現代社会とうつ病（最終回）新しいうつ病治療の可能性

◆トップランナーに聞く(48) 肺炎の原因微生物を探求して
ーより迅速に，より安価に，より正確にー

◆ノーベル賞と医学の進歩・発展(27) 自然免疫機構の解明

◆トピックス 慢性閉塞性肺疾患の呼吸困難に対する
鍼治療の臨床効果について

◆第51回（2014年度）ベルツ賞受賞論文ー1等賞 掲載

1 2015