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研究成果の刊行物・別刷

Geriatr Gerontol Int 2014; **14 (Suppl. 1):** *122–128*

ORIGINAL ARTICLE

Use of alfacalcidol in osteoporotic patients with low muscle mass might increase muscle mass: An investigation using a patient database

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Aim: Sarcopenia causes a decline in physical performance and decreased quality of life. However, there is little evidence for effective treatments. Because of the similarities between osteoporosis and sarcopenia, alfacalcidol used for osteoporosis might be beneficial for low muscle mass. Therefore, we investigated the effect of alfacalcidol on muscle mass in patients with low muscle mass.

Methods: In this retrospective cohort analysis, patients from an osteoporosis database were divided into two groups: alfacalcidol-treated patients (vitamin D group; $n = 156$) and a control group without drug treatment ($n = 233$). Muscle mass was evaluated in terms of the skeletal muscle index (SMI; kg/m^2) obtained from dual-energy X-ray absorptiometry measurements that were taken at the start and end of a 1-year period. Low muscle mass was determined using specific SMI cut-offs for Japanese individuals.

Results: Both the vitamin D group (mean age 73.7 ± 9.8 years) and the control group (mean age 72.3 ± 11.9 years) were primarily women ($n = 141$, 90.4%; $n = 189$, 81.1%, respectively). Low muscle mass was identified in 32.7% ($n = 51$) of the vitamin D group and 32.2% ($n = 75$) of the control group. The mean appendicular SMI in the vitamin D group did not change significantly over the 1-year period. The change was significant among the patients with low muscle mass (5.30 kg/m^2 *vs* 5.49 kg/m^2). The mean appendicular SMI in the control group decreased significantly over the 1-year period (6.09 kg/m^2 *vs* 5.99 kg/m^2). The change in the patients with low muscle mass was not significant.

Conclusions: The vitamin D group maintained muscle mass, and the SMI increased in patients with low muscle mass. Thus, the use of alfacalcidol might be effective in osteoporotic patients with low muscle mass. **Geriatr Gerontol Int 2014; 14 (Suppl. 1): 122–128.**

Keywords: aging, alfacalcidol, muscle strength, osteoporosis, sarcopenia.

Introduction

Sarcopenia, or the age-related decrease in muscle strength and mass,[1] is an important risk factor for disability in older adults.[2,3] Historically, there have been a number of diagnostic criteria proposed for sarcopenia. A unified consensus in the literature is pending, with the most recent reports agreeing that a decrease in muscle mass is an essential factor in sarcopenia.

Accepted for publication 26 November 2013.

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In addition, there might be a close connection between sarcopenia and osteoporosis. Correlations between muscle mass and bone mineral content have been reported,[4] and hormonal changes, decreased physical activity, reduced protein intake, and chronic inflammation are all pathological factors common to both sarcopenia and osteoporosis.[5–9]

Well-established drug treatments for sarcopenia are lacking. Because of the similarities between osteoporosis and sarcopenia, therapeutic drugs used for osteoporosis might also be beneficial for sarcopenia. Vitamin D, for which receptors exist in muscles,[10,11] is commonly used to treat osteoporosis. To our knowledge, previous studies have focused on the effect of the activated vitamin D formulation, alfacalcidol, on vitamin D

deficiency,[12] and there have been no reports of its effect on muscle mass in patients with sarcopenia. Therefore, the current study aimed at investigating the effect of alfacalcidol on muscle mass, the important diagnostic item in sarcopenia.

Methods

The National Center for Geriatrics and Gerontology osteoporosis database was accessed for the present retrospective cohort study of 1283 patients who were suspected to have osteoporosis and underwent body tissue measurements using dual-energy X-ray absorptiometry (DXA) between 1992 and 2009.

A total of 389 patients who were treated with alfacalcidol (1.0 or 0.5 μg) during the 1-year period or whose condition was monitored during the 1-year period without drug treatment were recruited from this database. We isolated two groups who were both assessed by DXA at the initial measurement and again 1 year later: a vitamin D group ($n = 156$), who were treated with alfacalcidol (1.0 or 0.5 μg) during the 1-year period, and a control group ($n = 233$), whose condition was monitored during the 1-year period without drug treatment.

Body composition was measured using whole-body DXA (DXP-NT; GE Medical Systems Lunar, Madison, WI, USA). Bone mineral content, fat mass and lean soft-tissue mass were measured separately for each part of the body, including the arms and legs. The lean soft-tissue mass of the arms and legs was nearly equal to the skeletal muscle mass. Therefore, in the present study, appendicular muscle mass is defined as the sum of the arm lean mass and the leg lean mass, and leg muscle mass is defined as the leg lean mass.

The appendicular SMI is calculated as appendicular muscle mass divided by the square of height, and the leg SMI is leg muscle mass divided by the square of height.

According to Baumgartner *et al.*, the appendicular SMI cut-off values for sarcopenia are <7.26 kg/m^2 for men and <5.45 kg/m^2 for women;[13] however, Sanada *et al.* reported that the SMI cut-off values for sarcopenia in Japanese individuals are <6.87 kg/m^2 for men and <5.46 kg/m^2 for women.[14] The latter cut-offs, specific for Japanese individuals, were used as low muscle mass in this study.

Statistical analysis

Appendicular SMI, leg SMI, total bone density and total fat mass were analyzed for the two groups, and a further analysis was carried out for patients with and without low muscle mass independently of the groups. A χ^2-test was carried out for categorical data (sex and the prevalence of low muscle mass), and Student's *t*-tests were carried out for the comparison of continuous data. A paired *t*-test was used to compare data

between the initial measurement and the follow up 1 year later for the various groups. Logistic regression analysis was carried out to show the intergroup differences of the changes from the initial measurement to the measurement 1 year later.

SPSS (v20.0; IBM Corp., Armonk, NY, USA) was used to carry out the statistical analysis, and statistical significance was set at $P < 0.05$.

Results

Table 1 provides the data for the vitamin D and control groups at the initial measurement. The mean age of the vitamin D group was 73.7 ± 9.8 years. The majority (90.4%, $n = 141$) were women, and 32.7% ($n = 51$) met the criteria for low muscle mass. The mean age of the control group was 72.3 ± 11.9 years. The majority (81.1%, $n = 189$) were also women, and a similar percentage (33.2%, $n = 75$) had low muscle mass.

There were significant differences between the groups in sex, whole-body bone mineral content, appendicular muscle mass, leg muscle mass and appendicular SMI at the time of the initial measurement (Table 1).

Appendicular SMI

The mean appendicular SMI in the vitamin D group did not change significantly from the initial measurement (5.87 kg/m^2) to the measurement 1 year later (5.88 kg/m^2). The mean appendicular SMI in the control group decreased significantly from 6.09 kg/m^2 at the initial measurement to 5.99 kg/m^2 1 year later ($P < 0.05$; Table 2).

The mean appendicular SMI of women in the vitamin D group did not change significantly from the initial measurement (5.87 kg/m^2) to the measurement 1 year later (5.85 kg/m^2). The mean appendicular SMI in the control group decreased significantly from 6.09 kg/m^2 at the initial measurement to 5.83 kg/m^2 1 year later ($P < 0.05$; Table 3).

In patients with low muscle mass, the mean appendicular SMI in the vitamin D group increased significantly from 5.30 kg/m^2 at the initial measurement to 5.49 kg/m^2 1 year later ($P < 0.05$). However, the mean appendicular SMI in the control group did not change significantly from the initial measurement (5.23 kg/m^2) to the measurement 1 year later (5.30 kg/m^2; Table 4).

In female patients with low muscle mass, the mean appendicular SMI in the vitamin D group increased significantly from 5.07 kg/m^2 at the initial measurement to 5.30 kg/m^2 1 year later ($P < 0.05$). However, the mean appendicular SMI in the control group did not change significantly from the initial measurement (4.90 kg/m^2) to the measurement 1 year later (5.03 kg/m^2; Table 5).

Table 1 Demographic and clinical characteristics of the participants from the National Center for Geriatrics and Gerontology osteoporosis database, compared between the vitamin D (receiving alfacalcidol treatment) and the control group

Characteristics	Vitamin D group (n = 156)	Control group (n = 233)	P-value
Sex (male/female)	15/141	44/189	0.012
Age (years)	73.7 ± 9.8	72.4 ± 11.9	NS
Height (cm)	150.1 ± 7.8	151.4 ± 9.1	NS
Weight (kg)	48.7 ± 8.7	50.1 ± 11.2	NS
Whole-body bone mineral content (g)	1489 ± 294	1649 ± 497	0.0003
Whole-body fat tissue mass (g)	14,187 ± 6568	13,161 ± 7875	NS
Appendicular lean mass (g)	13,258 ± 2018	14,073 ± 3085	0.004
Leg lean mass (g)	10,179 ± 1556	10,704 ± 2299	0.013
Appendicular SMI (kg/m^2)	5.872 ± 0.690	6.091 ± 0.954	0.014
Leg SMI (kg/m^2)	4.508 ± 0.533	4.636 ± 0.716	NS
Prevalence of sarcopenia (%)	51 (32.7)	75 (32.2)	NS

All data, except sex and the prevalence of sarcopenia, are expressed as mean ± SD (n = 389). A χ^2-test was carried out to compare the sex distribution. Student's t-tests were used to compare the remaining variables. NS, not significant; SMI, skeletal muscle index.

Table 2 Clinical characteristics of the participants in the vitamin D and control groups, compared respectively between the time of the initial measurements and 1 year later

characteristics	Vitamin D group (n = 156)		P-value	Control group (n = 233)		P-value
	Baseline	One year		Baseline	One year	
Whole-body bone mineral content (g)	1489 ± 294	1473 ± 291	0.0082	1649 ± 497	1624 ± 521	0.0030
Whole-body fat tissue mass (g)	14187 ± 6568	14431 ± 6539	NS	13161 ± 7875	13506 ± 7844	0.0360
Appendicular lean mass (g)	13258 ± 2018	13283 ± 2014	NS	14073 ± 3085	13862 ± 3284	0.0356
Leg lean mass (g)	10179 ± 1556	10128 ± 1510	NS	10704 ± 2299	10519 ± 2469	0.0103
Appendicular SMI (kg/m^2)	5.87 ± 0.690	5.88 ± 0.680	NS	6.09 ± 0.954	5.99 ± 1.020	0.0258
Leg SMI (kg/m^2)	4.51 ± 0.533	4.49 ± 0.513	NS	4.64 ± 0.716	4.55 ± 0.791	0.0075

All data are expressed as mean ± SD (n = 389). Paired t-tests were used to compare all variables. NS, not significant; SMI, skeletal muscle index.

In addition, assessed by logistic regression analysis to correct the baseline parameters, the intergroup difference of the changes of appendicular SMI from the initial measurement to the measurement 1 year later showed the borderline significance (P = 0.07).

Leg SMI

The mean leg SMI in the vitamin D group did not change significantly from the initial measurement (4.51 kg/m^2) to the measurement 1 year later (4.49 kg/m^2). The mean leg SMI in the control group decreased significantly from 4.64 kg/m^2 at the initial measurement to 4.55 kg/m^2 1 year later (P < 0.05; Table 2).

The mean leg SMI of women in the vitamin D group did not change significantly from the initial measurement (4.51 kg/m^2) to the measurement 1 year later (4.47 kg/m^2). The mean leg SMI in the control group decreased significantly from 4.64 kg/m^2 at the initial measurement to 4.46 kg/m^2 1 year later (P < 0.05; Table 3).

In patients with low muscle mass, the mean leg SMI of the vitamin D group increased significantly from 4.08 kg/m^2 at the initial measurement to 4.19 kg/m^2 1 year later (P < 0.05). The mean leg SMI of the control group increased from 3.99 kg/m^2 at the initial measurement to 4.03 kg/m^2 1 year later, but this change was not statistically significant (Table 4).

Table 3 Clinical characteristics of the female participants in the vitamin D and control groups, compared respectively between the time of the initial measurements and 1 year later

Characteristics	Females Vitamin D group (n = 141)		P-value	Control group (n = 189)		P-value
	Baseline	One year		Baseline	One year	
Whole-body bone mineral content (g)	1447 ± 274	1434 ± 272	0.0251	1525 ± 412	1499 ± 442	0.007
Whole-body fat tissue mass (g)	14346 ± 6549	14728 ± 6472	0.0426	13181 ± 8262	13348 ± 8200	NS
Appendicular lean mass (g)	12945 ± 1711	12968 ± 1705	NS	13220 ± 2400	12995 ± 2572	0.0483
Leg lean mass (g)	9962 ± 1342	9916 ± 1302	NS	10144 ± 1878	9993 ± 2052	0.0100
Appendicular SMI (kg/m^2)	5.87 ± 0.690	5.85 ± 0.653	NS	6.09 ± 0.954	5.83 ± 0.933	0.0390
Leg SMI (kg/m^2)	4.51 ± 0.533	4.47 ± 0.492	NS	4.64 ± 0.716	4.46 ± 0.759	0.0083

All data are expressed as mean ± SD (n = 330). Paired t-tests were used to compare all variables. NS, not significant; SMI, skeletal muscle index.

Table 4 Clinical characteristics of patients with low muscle mass in the vitamin D and control group, compared respectively between the time of the initial measurements and 1 year later

Characteristics	Vitamin D group (n = 51)		P-value	Control group (n = 75)		P-value
	Baseline	One year		Baseline	One year	
Whole-body bone mineral content (g)	1504 ± 340	1498 ± 330	NS	1575 ± 506	1546 ± 515	0.0134
Whole-body fat tissue mass (g)	12738 ± 7041	12705 ± 7042	NS	11048 ± 7131	11408 ± 7636	NS
Appendicular lean mass (g)	12603 ± 2350	13024 ± 2313	0.0031	12276 ± 2840	12430 ± 3048	NS
Leg lean mass (g)	9688 ± 1804	9926 ± 1744	0.0372	9339 ± 2104	9463 ± 2343	NS
Appendicular SMI (kg/m^2)	5.30 ± 0.594	5.49 ± 0.642	0.0017	5.23 ± 0.819	5.30 ± 0.946	NS
Leg SMI (kg/m^2)	4.08 ± 0.468	4.19 ± 0.490	0.0255	3.99 ± 0.624	4.03 ± 0.773	NS

All data are expressed as mean ± SD (n = 126). Paired t tests were used to compare all variables. NS, not significant; SMI, skeletal muscle index.

Table 5 Clinical characteristics of female patients with low muscle mass in the vitamin D and control group, compared respectively between the time of the initial measurements and 1 year later

Characteristics	Females Vitamin D group (n = 38)		P-value	Control group (n = 52)		P-value
	Baseline	One year		Baseline	One year	
Whole-body bone mineral content (g)	1377 ± 283	1381 ± 278	NS	1388 ± 418	1355 ± 414	0.0215
Whole-body fat tissue mass (g)	12816 ± 7108	13117 ± 7153	NS	10964 ± 7857	10840 ± 8270	NS
Appendicular lean mass (g)	11532 ± 1190	12057 ± 1349	0.0003	10875 ± 1946	11176 ± 2355	NS
Leg lean mass (g)	8919 ± 902	9264 ± 1085	0.0028	8407 ± 1552	8916 ± 2036	NS
Appendicular SMI (kg/m^2)	5.07 ± 0.342	5.30 ± 0.453	0.0003	4.90 ± 0.664	5.03 ± 0.895	NS
Leg SMI (kg/m^2)	3.92 ± 0.241	4.07 ± 0.355	0.0029	3.79 ± 0.557	3.88 ± 0.799	NS

All data are expressed as mean ± SD (n = 90). Paired t-tests were used to compare all variables. NS, not significant; SMI, skeletal muscle index.

In female patients with low muscle mass, the mean leg SMI of the vitamin D group increased significantly from 3.92 kg/m^2 at the initial measurement to 4.07 kg/m^2 1 year later ($P < 0.05$). The mean leg SMI of the control group increased from 3.79 kg/m^2 at the initial measurement to 3.88 kg/m^2 1 year later, but this change was not statistically significant (Table 5).

In addition, assessed by logistic regression analysis to correct the baseline parameters, the intergroup difference of the changes of leg SMI from the initial

measurement to the measurement 1 year later was not statistically significant.

Whole-body bone mineral content

The mean total bone mineral content decreased from 1489 g at the initial measurement to 1473 g 1 year later in the vitamin D group, and from 1649 g at the initial measurement to 1624 g 1 year later in the control group; this was a significant difference in both cases ($P < 0.05$; Table 2).

In patients with low muscle mass, the mean bone mass of the vitamin D group was 1504 g at the initial measurement and 1498 g 1 year later, and this difference was not statistically significant. The mean bone mass of the control group decreased significantly from 1575 g at the initial measurement to 1546 g 1 year later ($P < 0.05$; Table 4).

Whole-body fat tissue mass

The mean total fat mass of the vitamin D group increased from 14 187 g at the initial measurement to 14 431 g 1 year later, but this change was not statistically significant. The mean fat mass of the control group decreased significantly from 13 161 g at the initial measurement to 13 506 g 1 year later ($P < 0.05$; Table 2).

In patients with low muscle mass, the mean fat mass was 12 738 g at the initial measurement and 12 705 g 1 year later in the vitamin D group, and 11 048 g at the initial measurement and 11 408 g 1 year later in the control group. The changes in both groups were not statistically significant (Table 4).

Discussion

To our knowledge, this is the first study to report an association between the administration of activated vitamin D and increased muscle mass in patients with low muscle mass, whereas previous studies have only reported that activated vitamin D acts to increase muscle strength and decrease the risk of falls.[15,16]

The link between vitamin D and fall risk reported by the previous studies could be a result of factors that affect neuromuscular function.[17,18] However, considering the previous reports that muscle mass and muscle strength were positively correlated,[19] and muscle strengthening decreased fall risk,[22] muscle strength reinforcement by the effect of increasing muscle mass by the administration of activated vitamin D might be one of the factors to decrease fall risk by the administration of vitamin D.

In the current study, maintenance of muscle mass occurred in the vitamin D group, whereas a significant decrease occurred in the control group. This effect was particularly pronounced in patients with low muscle mass receiving alfacalcidol, who experienced a significant increase in muscle mass, suggesting that alfacalcidol might act to increase muscle mass.

It is known that D-hormone receptors are expressed in muscle.[11] In D-hormone receptor knockout mice, differentiation into normal myocytes cannot take place, which results in the formation of small myocytes. Activated vitamin D counteracts this abnormality of myogenic cells.[21] Because D-hormone receptor expression decreases in myocytes with advancing age,[22] decreased D-hormone receptor expression was likely present in the patients in this study.

Elevated interleukin (IL)-6 and tumor necrosis factor (TNF)-α levels also reduce D-hormone receptor activity, even in the presence of adequate vitamin D.[23] Unlike inactive vitamin D, alfacalcidol effectively improves this vitamin D resistance.[24] Furthermore, muscle mass tends to be lower when IL-6 and TNF-α are elevated.[25] It is not uncommon for increased levels of these cytokines to be present in older adults[21] and in sarcopenia.[26] According to Zhang *et al.*, administration of alfacalcidol to vitamin-D-deficient patients decreases levels of IL-6 and TNF-α secreted by lipopolysaccharide-stimulated human monocytes.[27] Therefore, alfacalcidol might improve vitamin D resistance relating to both D-hormone receptor and cytokine activity, and this could explain the differences between the groups, as well as the improvements observed in the patients with low muscle mass in the current study. This is in addition to the effects of alfacalcidol on vitamin D levels, when it has been reported that low 25(OH)D levels could increase the risk of sarcopenia.[28] The 25(OH)D levels of patients with low muscle mass in the present study are unknown, but it is likely that they were lower than the 25(OH)D levels in the patients with normal muscle mass.

Type II muscle fibers are predominantly lost in sarcopenia,[29] and vitamin D might also be effective against this loss. It has been reported that treatment with alfacalcidol increases type II muscle fibers,[24] and the diameter of type II muscle fibers measured using muscle biopsy increases after vitamin D administration.[30]

There were some limitations that warrant attention. The first limitation was the retrospective study design. The participants in vitamin D group were diagnosed with osteoporosis. In contrast, the participants in the control group were not diagnosed with osteoporosis or were not able to take alfacalcidol for some reason. As a result, there was a significant difference in bone mineral content and muscle mass at the baseline between the vitamin D group and the control group. Therefore, it was difficult to compare the vitamin D group and the control group to correct the baseline. In fact, we carried out logistic regression analysis with the independent

variables as bone mineral content at baseline and the treatment or no treatment with alfacalcidol, and the dependent variable as the increase or decrease of appendicular SMI, but the result was that the efficiency of alfacalcidol to appendicular SMI was on the borderline ($P = 0.07$). Therefore, we need to carry out a prospective study to adjust the baseline demographics and compare the vitamin D group with the control group. The second limitation was that the vitamin D status of the patients was unknown. We did not measure 25(OH)D or intact parathyroid hormone, and the use of other drugs was not known.

In conclusion, the present study showed that patients who received alfacalcidol treatment maintained their muscle mass, and the patients with low muscle mass who received alfacalcidol treatment experienced increases in their muscle mass. This suggests that alfacalcidol might be effective in sarcopenic patients.

Acknowledgments

This study was funded in 2010 by a Comprehensive Research on Aging and Health research grant from the Ministry of Health, Labor and Welfare of Japan. No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Disclosure statement

The authors declare no conflict of interest.

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Geriatr Gerontol Int 2013; 13: 413–420

ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

High prevalence of sarcopenia and reduced leg muscle mass in Japanese patients immediately after a hip fracture

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Aim: Sarcopenia-related falls and fractures are becoming an emerging problem as a result of rapid aging worldwide. We aimed to investigate the prevalence of sarcopenia by estimating the muscle mass of the arms and legs of patients with and without hip fracture.

Methods: This cross-sectional study examined 357 patients immediately after a hip fracture (the HF group) and in 2511 patients from an outpatient clinic who did not have a hip fracture (the NF group) at single institution in Japan. We carried out whole-body dual energy X-ray absorptiometry to analyze body composition with skeletal muscle mass index (SMI; lean mass / height^2) and bone mineral density (BMD). We carried out stepwise logistic regression analysis to determine the factors associated with a hip fracture.

Results: Lower appendicular SMI ($P < 0.001$), leg SMI ($P < 0.001$), and higher prevalence of sarcopenia ($P < 0.001$) were observed in the HF group after controlling for age and sex. The arm SMI was similar in both groups ($P > 0.95$). In multivariate analysis, the presence of sarcopenia, older age and lower BMD were associated with the occurrence of a hip fracture (OR 1.476, $P = 0.002$; OR 1.103, $P < 0.001$; OR 0.082, $P < 0.001$; respectively).

Conclusion: This study showed a higher prevalence of sarcopenia and more reduced leg muscle mass in patients after a hip fracture than in the outclinic patients who did not have hip fractures. The results imply sarcopenia can be a risk factor for a hip fracture. **Geriatr Gerontol Int 2013; 13: 413–420.**

Keywords: dual energy X-ray absorptiometry, hip fracture, osteoporosis, sarcopenia, skeletal muscle mass.

Introduction

As populations are aging worldwide, the number of patients with osteoporotic fracture is increasing. Hip fracture, which is the most common osteoporotic fracture, is one of the most serious and unavoidable medical and social concerns.[1] A fracture of the hip results in increased mortality, persistent physical morbidity[2] and limited activities of daily living (ADL).[3] It is also associated with a high risk of institutionalization,[4,5] readmission[6] and reduction of the quality of life for caregivers.[7] The financial burden on society is becoming more and more critical.[8] Prevention of hip fracture is essential for maintaining a good quality of life for the elderly.

Accepted for publication 12 June 2012.

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The role of muscles in maintaining functional performance and preventing falls has been an emphasis in recent years. The mass and strength of skeletal muscles decrease with age, and this loss accelerates after 65 years-of-age with a risk of adverse outcomes, such as physical disability, poor quality of life and death.[9] This condition, called sarcopenia, has received particular attention in recent years.[10,11] In addition to a decrease of physical performance, the elderly with sarcopenia have increased risk of age-related diseases, such as decreased swallowing function[12] or urinary disorder, as a result of muscle dysfunction.[13] Consequently, sarcopenia is regarded as an indicator of development of frailty[14] and loss of independence in the elderly. Furthermore, this condition is also associated with increased physical disabilities, resulting in the risk of falls.[15] However, the impact of sarcopenia on osteoporotic fractures has rarely been reported.

The aim of the present study was to estimate the muscle volume of the extremities and investigate the prevalence of sarcopenia in patients immediately after the occurrence of a hip fracture.

doi: 10.1111/j.1447-0594.2012.00918.x

Methods

The present cross-sectional study examined the reduction of muscle mass of patients with or without hip fracture. Between June 2002 and January 2009, all patients with a fresh hip fracture who were at least 55 years-of-age and admitted to a single study institution in Japan were eligible and assigned to the hip fracture group (HF group). Exclusion criteria were the refusal to give informed consent or inability to carry out whole-body dual energy X-ray absorptiometry (DXA) within 48 h of admission. DXA evaluation, not only of the lumbar spine or hip regions, but also of the whole body, was routinely applied for the diagnosis of osteoporosis at the study institution. Patients who visited the outpatient clinic of the study institution and received DXA during the same period were assigned to the non-fracture group (NF group) if they had no previous history of hip fracture. The study protocol was approved by the Institutional Review Board of the National Center for Geriatrics and Gerontology, and all patients gave detailed written informed consent.

During the study period, 422 acute hip fracture patients aged 55 years and older were admitted to the study institution. Of these patients, 34 (8.1%) were excluded because there was no time to carry out DXA preoperatively due to the need for urgent surgical repair, and 31 (7.3%) were excluded because they or their family were unable to give informed consent. The final study population of 357 participants for the HF group (304 females, 82.7 ± 9.3 years and 53 males, 80.3 ± 9.4 years) did not differ significantly from the non-participants with regard to age, sex, height or bodyweight. During the same period, 2816 consecutive patients aged over 55 years without a history of hip fracture visited the outpatient clinic of the same study institution to check their bone mineral density (BMD) by DXA. Of these patients, 305 were excluded from the study because they received only lumbar or hip DXA and lacked the data of whole-body DXA. Finally, 2511 patients (1893 females, 70.5 ± 11.1 years and 618 males, 67.5 ± 11.6 years) received whole-body DXA and were assigned to the NF group.

Body composition was measured by whole-body DXA (DPX-NT; GE Medical Systems Lunar, Madison, WI, USA). Bone mineral content, fat mass and lean soft-tissue mass were measured separately for each part of the body, including the arms and legs. The lean soft-tissue masses of the arms and legs were nearly equal to the skeletal muscle mass. As absolute muscle mass correlates with height, the skeletal muscle mass index was calculated by the following formula: lean mass (kg) / height^2 (m^2), which is directly analogous to body mass index (BMI; weight [kg]/height^2 [m^2]). Arm skeletal muscle mass index (arm SMI) was defined as (arm lean mass [kg]/height^2 [m^2]). Leg skeletal muscle mass index (leg SMI) was defined as (leg lean mass [kg]/height^2 [m^2]). Appendicular skeletal muscle mass index (appendicular SMI) was defined as the sum of the arm SMI and the leg SMI.[16] Appendicular SMI is commonly used to assess muscle mass in various sarcopenic studies.[9] Sarcopenia was defined according to the criteria for the Japanese based on the report by Sanada *et al.* [7] The value of the Japanese criterion was calculated as below two standard deviations (SD) of the mean appendicular SMI of 569 Japanese healthy volunteers whose ages ranged from 18 to 40 years. The criterion value was an appendicular SMI below 5.46 kg/m^2 in women and below 6.87 kg/m^2 in men. We simultaneously measured the BMD of the whole body, including the lumbar spine, by DXA for all of the participants in the present study.

We used Mann–Whitney's *U*-test to estimate the patient characteristics between the study groups. To compare the prevalence of sarcopenia, we carried out χ^2-test and Fisher's exact test. To find a significant relationship between appendicular SMI and BMD, Pearson's correlation was carried out in each group. We evaluated the appendicular SMI value on continuous variables by using a general linear model to control with covariates as age and sex.[18] The general linear model is a generalization of multiple linear regression model to the case of more than one dependent variable.[19,20] Prevalence of sarcopenia was calculated according to four age groups (age less than 70 years, between 70 years to 74 years, between 75 years to 80 years, more than 80 years). The Mantel–Haenszel method was used for testing significance for age–sex adjusted prevalence of sarcopenia.

To determine the presence of the sarcopenia as an independent variable in predicting the occurrence of hip fracture selected as dependent variables, we used the stepwise multiple logistic regression model. The regression model also included the patient characteristics of age, sex, whole body BMD, weight and height, which were known to be the key predictors for skeletal muscle mass.[18] The strength of association of the chosen variables and the occurrence of hip fracture was reported as the odds ratio (OR) and 95% confidential intervals (CI) in relation to a reference group.

Statistical analyses were carried out using SPSS for Windows software (version 19.0; SPSS, Chicago, IL, USA). A *P*-value of <0.05 was considered significant.

Results

Table 1 shows the characteristics, body composition and skeletal muscle mass index of the patients included in the present study. All the patients (both men and women) in the HF group were older adults. The height, weight and BMI were significantly lower in the HF