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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.

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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

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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.

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Disclosure statement

The authors declare no conflict of interest.

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