

The effects of minodronate and activated vitamin D on bone mineral density and muscle mass in postmenopausal women with osteoporosis

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Abstract:

Introduction: Osteoporosis and sarcopenia are said to be similar disorders. However, few reports have described the effects of anti-osteoporosis drugs on muscle mass in clinical practice.

Methods: We selected 150 postmenopausal women with osteoporosis treated by minodronate (osteoporosis medication [OM] group) and 50 postmenopausal women without osteoporosis who did not receive treatment (no osteoporosis [NO] group). The OM group was further divided into two treatment subgroups: a combination of monthly minodronate and daily activated vitamin D vs. monthly minodronate alone. We measured lumbar spine and femoral neck bone mineral density (BMD) with dual-energy X-ray absorptiometry and muscle mass of the upper limbs, lower limbs, and trunk with bioelectrical impedance analysis at baseline and after 6 months.

Results: The OM and NO groups contained 130 and 37 patients, respectively (mean age: 73.9 ± 8.3 and 74.1 ± 10.0 years, respectively). In the OM group, lumbar spine BMD significantly increased after 6 months, while lower limb muscle mass significantly decreased. In the NO group, lumbar spine BMD and lower limb muscle mass did not significantly change after 6 months. In the OM group, BMD of the lumbar spine significantly increased but the lower limb muscle mass significantly decreased after 6 months relative to the NO group. In the combination therapy subgroup of the OM group muscle mass decreased significantly less than in the minodronate-alone subgroup.

Conclusions: In postmenopausal women with osteoporosis, minodronate can increase BMD but cannot increase muscle mass. However, simultaneous use of activated vitamin D can suppress muscle mass decrease. The combination of activated vitamin D and minodronate may be useful for treating osteoporosis in postmenopausal women.

Keywords:

osteoporosis, sarcopenia, bone mineral density, minodronate, activated vitamin D, muscle mass, postmenopausal

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Introduction

Osteoporosis and sarcopenia are said to be similar disorders¹⁾.

According to a report from Finland, women with sarcopenia suffered from osteoporosis 13 times more often than women without sarcopenia, and osteoporosis was found to

be 12 times more frequent in the weak grip strength (weak muscular strength) group than in the strong grip strength (strong muscular strength) group²). However, there is a large gap between these disorders in terms of treatment. There are various drugs that effectively treat osteoporosis. In contrast, it is currently unclear whether there are curative drugs for sarcopenia. Increases in grip strength and bone mineral density (BMD) were recognized in a study of a therapy with alendronate and calcitriol in postmenopausal women³). A study on activated vitamin D revealed that muscle mass could be maintained by administering alfacalcidol to patients with osteoporosis⁴). Moreover, muscle fiber diameter was increased by administering a low amount of vitamin D in women who had experienced cerebral infarction⁵). Because osteoporosis and sarcopenia are similar disorders, the same drugs (e.g., bone resorption inhibitors and activated vitamin D) might effectively treat both disorders. However, only a few reports describe the actual use of these drugs in clinical practice.

Thus, we conducted this study to investigate how muscle mass of the upper limbs, lower limbs, and trunk changes over a period of 6 months during administration of minodronate, a bisphosphonate and a common bone resorption inhibitor, in patients with osteoporosis. Furthermore, we investigated whether simultaneous administration of activated vitamin D affected the results.

Materials and Methods

Study subjects

Participants were selected from postmenopausal women with osteoporosis who visited our hospital during the 19-month period between April 15, 2015 and November 15, 2016. The osteoporosis medication (OM) group contained 150 such patients who met the diagnostic criteria for osteoporosis and consented to undergo osteoporosis drug treatment and bone densitometry and body composition measurements every 6 months. These criteria included (1) the diagnostic criteria for primary osteoporosis according to the guideline of the Japan Osteoporosis Society and (2) a BMD (of either the lumbar spine or femoral neck) 2.5 standard deviations or less from the mean (T -score ≤ -2.5). We also selected 50 patients for the no osteoporosis (NO) group. These patients did not meet the osteoporosis diagnostic criteria, were not treated with drugs for osteoporosis, and consented to undergo bone densitometry and body composition measurements every 6 months. We excluded patients who (1) had difficulty maintaining a standing position because of pain, paralysis, or scoliokyphosis, (2) had a pacemaker, and (3) were obese (body mass index [BMI] >30).

The OM group was further divided into two treatment subgroups: a combined therapy subgroup ($n = 75$, patients received a combination of minodronate [50 mg monthly] and activated vitamin D [0.75 μ g of eldcalcitol daily or 1 μ g of alfacalcidol daily]) and a minodronate (50 mg monthly) alone subgroup ($n = 75$).

Bone densitometry and body composition measurements were conducted at our orthopedic outpatient clinic. The study protocol was approved by the local ethics committee, and all patients provided written informed consent.

Study procedure and equipment

During the semi-annual outpatient visits, we measured BMD of the lumbar spine and femoral neck with dual-energy X-ray absorptiometry (Lunar DPK-BRAVO, GE Healthcare, Tokyo, Japan) and muscle mass of the upper limbs, lower limbs, and trunk with bioelectrical impedance analysis (BIA; In Body 720 Biospace device, Biospace Co., Ltd., Seoul, South Korea), with the patient in a standing position. The BIA instrument determined fat and fat-free masses of the upper and lower limbs and trunk based on the relationship between conductance and electrical resistance. Eight electrodes were used to apply a weak electrical current.

Endpoints

Primary endpoint: can muscle mass be increased by administration of minodronate?

We examined changes from baseline at 6 months in BMD of the lumbar spine and femoral neck and muscle mass of the upper and lower limbs and trunk and compared these changes between the OM group and the NO group.

Secondary endpoint: differences in the effects of minodronate alone and minodronate combined with activated vitamin D

We examined whether there were significant differences in age, BMI, and BMD of the lumbar spine and femoral neck, as well as in muscle mass of the upper and lower limbs and trunk, at baseline between the two subgroups of the OM group. Moreover, differences in BMD of the lumbar spine and femoral neck and muscle mass of the upper and lower limbs and trunk between baseline and 6 months of treatment were assessed in the two subgroups.

Statistical analysis

A paired t -test was used to determine significance of temporal changes in BMD and muscle mass. Significance of differences between the two subgroups was determined with Mann-Whitney's U test. p -Values <0.05 were considered to indicate a statistically significant difference.

Results

Subjects

After excluding 33 patients who discontinued the treatment or withdrew from the study, data of 167 patients were analyzed. There were 130 patients in the OM group and 37 patients in the NO group.

In the OM group, the mean administration period of mi-

Table 1. Clinical Characteristics at Baseline in the Osteoporosis Medication (OM) Group and the No Osteoporosis (NO) Group.

Characteristic	OM (n=130)	NO (n=37)	p-value
Age, years	73.9±8.3	74.1±10.0	0.9
Body mass index, kg/m ²	21.3±2.9	22.2±3.2	0.1
Bone mineral density, g/cm ²			
Lumbar spine	0.91±0.14	0.98±0.15	0.02*
Femoral neck	0.66±0.08	0.69±0.07	0.01*
Muscle mass, kg			
Upper limbs	2.96±0.49	3.01±0.55	0.6
Lower limbs	9.89±1.48	10.03±1.67	0.6
Trunk	14.48±1.61	14.65±1.83	0.6

*: Statistical significance (p<0.05)

Table 2. BMD and Muscle Mass at Baseline and after 6 Months of Treatment in the Osteoporosis Medication (OM) Group (n=130) and the No Osteoporosis (NO) Group (n=37).

		Baseline	6 months	p-value
		BMD, g/cm ²		
Lumbar spine	OM	0.91±0.14	0.92±0.14	<0.0001*
	NO	0.98±0.15	0.97±0.15	0.5
Femoral neck	OM	0.66±0.08	0.66±0.08	0.08
	NO	0.69±0.07	0.69±0.08	0.7
		Muscle mass, kg		
Upper limbs	OM	2.95±0.47	2.94±0.52	0.3
	NO	3.01±0.55	2.98±0.59	0.4
Lower limbs	OM	9.89±1.48	9.66±1.45	<0.0001*
	NO	10.03±1.67	10.00±1.66	0.7
Trunk	OM	14.48±1.61	14.49±1.60	0.7
	NO	14.65±1.83	14.55±1.90	0.2

BMD, bone mineral density.

*: Statistical significance (p<0.05)

nodronate at baseline was 8.1 ± 5.3 months. There were no cases of minodronate administration for more than 2 years. Patients who had been treated with another anti-osteoporosis drug in the past started to receive minodronate after at least a 3-month break. The patients did not exercise regularly.

The baseline data of the OM and NO groups are shown in Table 1. The mean age of patients in the OM group was 73.9 ± 8.3 years, and that of patients in the NO group was 74.1 ± 10.0 years, with no significant difference ($p = 0.9$). The BMDs of both the lumbar spine and femoral neck were significantly greater in the NO group than in the OM group (lumbar spine: $p = 0.02$, femoral neck: $p = 0.01$; Table 1).

Endpoints

Primary endpoint: Can muscle mass be increased by administration of minodronate?

In the OM group, the BMD of the lumbar spine was significantly higher at 6 months (0.92 ± 0.14 g/cm²) than at baseline (0.91 ± 0.14 g/cm²; $p < 0.0001$), while the muscle mass of the lower limbs was significantly reduced after 6

months (9.66 ± 1.45 kg) compared with baseline (9.89 ± 1.48 kg; $p < 0.0001$). The rates of change were 1.7% for BMD of the lumbar spine and -2.3% for muscle mass of the lower limbs. In contrast, in the NO group, there were no significant changes in BMD of the lumbar spine (0.97 ± 0.15 g/cm²) vs. baseline (0.98 ± 0.15 g/cm²; $p = 0.5$) and in muscle mass of the lower limbs (10.00 ± 1.66 kg) vs. baseline (10.03 ± 1.67 kg; $p = 0.7$). However, we also found that both BMD and muscle mass of the lower limbs tended to decline. The rate of change was -0.4% for BMD of the lumbar spine and -0.3% for muscle mass of the lower limbs (Table 2).

With regard to the difference in changes of BMD and muscle mass between the two groups after 6 months of administration of minodronate, BMD of the lumbar spine significantly increased ($p = 0.002$), whereas muscle mass of the lower limbs significantly decreased ($p = 0.02$). There were no significant differences in BMD of the femoral neck ($p = 0.7$) and muscle mass of the upper limbs ($p = 0.9$) and trunk ($p = 0.2$) between the two groups (Fig. 1).

Secondary endpoint: differences in the effects of minodronate alone and minodronate combined with activated vitamin D

There were 60 patients in the combination therapy subgroup and 70 in the minodronate-alone subgroup. The characteristics of patients in the two subgroups at baseline are shown in Table 3. There were no statistically significant differences in age ($p = 0.4$), BMI ($p = 0.4$), BMD of the lumbar spine ($p = 1.0$) and femoral neck ($p = 0.9$), and muscle mass of the upper limbs ($p = 0.8$), lower limbs ($p = 0.2$), and trunk ($p = 0.8$). However, we found that the muscle mass of patients in the combination therapy subgroup decreased significantly less (-0.1569 kg) than that of patients in the minodronate-alone subgroup (-0.2943 kg; $p = 0.04$; Fig. 2).

Discussion

We conducted a prospective study of the effects of minodronate administration on muscle mass and BMD in post-

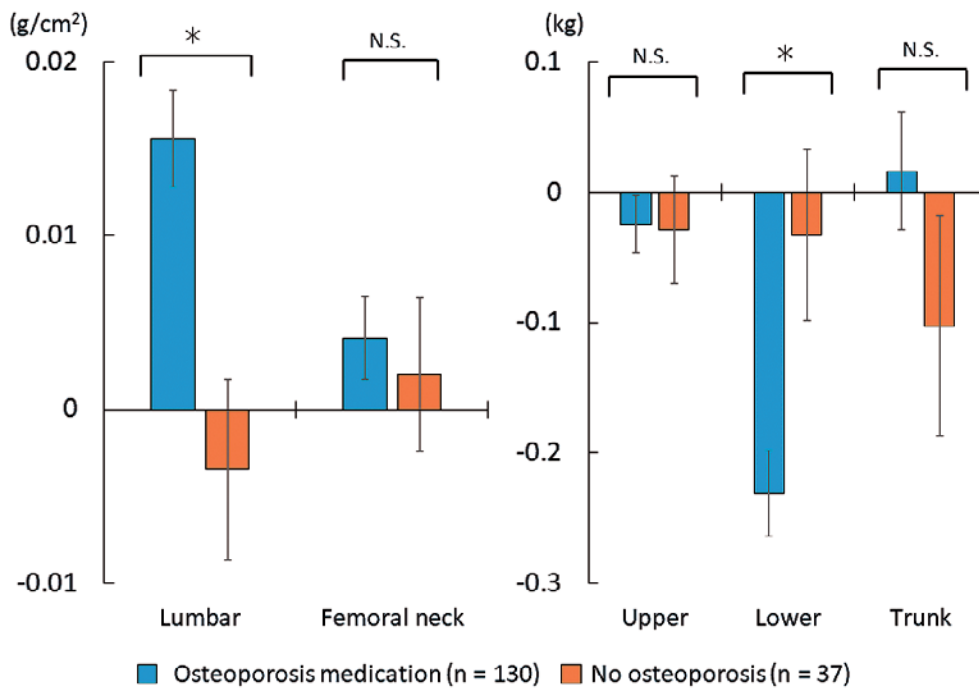


Figure 1. Changes in bone mineral density and muscle mass after 6 months of treatment between the osteoporosis medication group (n=130) and the no osteoporosis group (n=37).

Table 3. Clinical Characteristics at Baseline in the Combination of Minodronate and Activated Vitamin D Therapy Subgroup (n=60) and the Minodronate-alone Subgroup (n=70).

Medication	Combination	Minodronate alone	p-value
Age, years	73.2±8.4	74.5±8.2	0.4
Body mass index, kg/m ²	21.1±2.67	21.5±3.06	0.4
BMD, g/cm ²			
Lumbar spine	0.91±0.13	0.91±0.14	1.0
Femoral neck	0.66±0.09	0.66±0.07	0.9
Muscle mass, kg			
Upper limbs	2.95±0.47	2.97±0.52	0.8
Lower limbs	9.73±1.44	10.03±1.51	0.2
Trunk	14.43±1.55	14.52±1.68	0.8

menopausal women with osteoporosis. After 6 months of treatment, BMD of the lumbar spine significantly increased in the OM group, whereas muscle mass of the lower limbs significantly decreased. Muscle mass of the lower limbs also tended to decrease after 6 months in the NO group. Nevertheless, relative to the NO group, the OM group had significantly increased BMD of the lumbar spine and significantly decreased muscle mass of the lower limbs.

A study of about 4000 Japanese individuals revealed that muscle mass decreased with age especially strongly in the lower limbs⁶⁾. Age-related changes in the microenvironment of muscle tissue have been reported to reduce the muscle regeneration ability in rodent models^{7,8)}. In this regard, although bisphosphonate treats and prevents osteoporosis by suppressing osteoclastic bone resorption, it affects other cells as well. It was reported that alendronate could suppress migration, proliferation, and differentiation of undifferentiated

human muscle cells that are involved in muscle regeneration in vitro⁹⁾. A study on the combined use of alendronate and activated vitamin D in 38 Korean patients with osteoporosis in their 1950s found no tendency toward muscle mass increase³⁾. The following two possibilities should be considered with regard to the results of the current study. First, osteoporosis itself could accelerate the muscle mass decrease starting from the lower limbs. Second, minodronate administration could accelerate the muscle mass decrease. At the very least, we showed that minodronate did not induce muscle mass increase.

Furthermore, our analysis of the OM subgroups receiving minodronate combined with activated vitamin D or minodronate alone revealed that the decrease in the muscle mass of the lower limbs was significantly reduced in the combination therapy subgroup. It is known that vitamin D receptors are expressed in skeletal muscles, and activated vitamin D

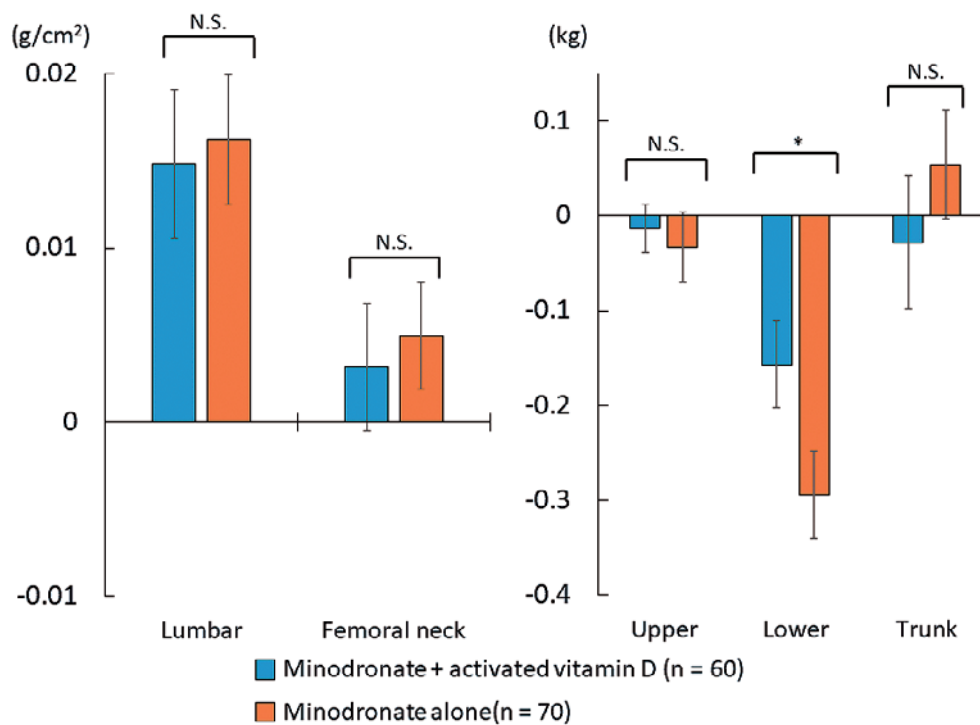


Figure 2. Changes in bone mineral density and muscle mass after 6 months of treatment between combination of minodronate and activated vitamin D therapy subgroup ($n=60$) and the minodronate-alone subgroup ($n=70$).

effectively maintains muscle mass. It has been reported that activated vitamin D supplementation prevented falls in the elderly¹⁰. In a prospective clinical study, alfacalcidol administration suppressed muscle mass decrease in patients with suspected osteoporosis compared with a control group, in which muscle mass decreased significantly after 1 year⁴. Therefore, activated vitamin D supplementation could suppress the decrease in muscle mass in the current study.

This study has some limitations. First, control groups of patients with osteoporosis receiving no anti-osteoporosis drugs or activated vitamin D only could not be used because of ethical concerns. Second, we did not evaluate whether the participants had vitamin D deficiency by measuring serum 25-hydroxy vitamin D (25 [OH] D) level. This was a consequence of limitations of the Japanese insurance system. Third, we did not evaluate daily physical activity levels. It has to be noted, however, that snowfall in winter is rare at our geographical location, suggesting that there were little changes in activity due to seasonal variations. Nevertheless, there is a possibility that differences in daily activity levels between patients with and without osteoporosis might lead to a significant difference in lower limb muscle mass decrease.

In conclusion, minodronate administration can increase BMD but cannot increase muscle mass in postmenopausal women with osteoporosis. Simultaneous use of activated vitamin D may suppress muscle mass decrease, and therefore, the combination of activated vitamin D and minodronate may be useful for treating osteoporosis.

Conflicts of Interest: The authors declare that there are no conflicts of interest.

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