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

Kazuki Fujimoto¹, Kazuhide Inage¹, Toru Toyoguchi¹, Yawara Eguchi¹, Sumihisa Orita¹, Kazuyo Yamauchi¹, Miyako Suzuki¹, Gou Kubota¹, Takeshi Sainoh¹, Jun Sato¹, Yasuhiko Shiga², Koki Abe³, Hirohito Kanamoto³, Masahiro Inoue⁴, Hideyuki Kinoshita³, Masaki Norimoto³, Tomotaka Umimura³, Masao Koda³, Takeo Furuya³, Junichi Nakamura³, Tsutomu Akazawa³, Atsushi Terakado³, Kazuhisa Takahashi³, and Seiji Ohtori³

¹) Department of Orthopaedic Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan
²) Department of Orthopaedic Surgery, Chiba Qiball Clinic, Chiba, Japan
³) Department of Orthopaedic Surgery, Shimoshizu National Hospital, Yotsukaido, Chiba, Japan
⁴) Department of Orthopaedic Surgery, Eastern Chiba Medical Center, Togane, Chiba, Japan
⁵) Department of Orthopaedic Surgery, Sainou Hospital, Toyama, Japan
⁶) Department of Orthopaedic Surgery, Chiba Aoba Municipal Hospital, Chiba, Japan
⁷) Department of Orthopaedic Surgery, St. Marianna University School of Medicine, Kawasaki, Japan
⁸) Department of Orthopaedic Surgery, Kitachiba Spine & Sports Clinic, Chiba, Japan

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

Corresponding author: Kazuki Fujimoto, s9082@nms.ac.jp
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be 12 times more frequent in the weak grip strength (weak muscular strength) group than in the strong grip strength (strong muscular strength) group. 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 women. A study on activated vitamin D revealed that muscle mass could be maintained by adminstering alfalcacitol to patients with osteoporosis. Moreover, muscle fiber diameter was increased by administering a low amount of vitamin D in women who had experienced cerebral infarction. 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 scoliosis, (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 μg of eldecalcitol daily or 1 μg of alfalcacitol 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-
nondronate at baseline was 8.1 ± 5.3 months. There were no cases of nondronate administration for more than 2 years. Patients who had been treated with another anti-osteoporosis drug in the past started to receive nondronate 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: 0.98 ± 0.15 g/cm² vs. baseline (0.97 ± 0.15 g/cm²; p = 0.5) and in muscle mass of the lower limbs (10.03 ± 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-

**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/m² | 21.3±2.9   | 22.2±3.2  | 0.1     |
| Bone mineral density, g/cm² | 0.91±0.14  | 0.98±0.15 | 0.02*   |
| 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/cm²    |          |          |         |
| Lumbar spine  | 0.91±0.14| 0.92±0.14| <0.0001*|
| Femoral neck  | 0.66±0.08| 0.69±0.08| 0.0001* |
| Upper limbs   | 2.95±0.47| 2.94±0.52| 0.3     |
| Lower limbs   | 9.89±1.48| 9.66±1.45| <0.0001*|
| Trunk         | 14.48±1.61| 14.49±1.60| 0.7     |

BMD, bone mineral density.

*: Statistical significance (p<0.05)
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. Never-
theless, relative to the NO group, the OM group had signifi-
cantly 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 limbs\textsuperscript{6}. Age-related changes in the microenvironment
of muscle tissue have been reported to reduce the muscle re-
generation ability in rodent models\textsuperscript{7,8}. In this regard, al-
though bisphosphonate treats and prevents osteoporosis by
suppressing osteoclastic bone resorption, it affects other cells
as well. It was reported that alendronate could suppress mi-
gregation, proliferation, and differentiation of undifferentiated
human muscle cells that are involved in muscle regeneration
in vitro\textsuperscript{9}. 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 in-
crease\textsuperscript{3}. The following two possibilities should be consid-
ered with regard to the results of the current study. First, os-
teoporosis itself could accelerate the muscle mass decrease
starting from the lower limbs. Second, minodronate admi-
istration could accelerate the muscle mass decrease. At the
very least, we showed that minodronate did not induce mus-
cle mass increase.

Furthermore, our analysis of the OM subgroups receiving
minodronate combined with activated vitamin D or minodro-
nate alone revealed that the decrease in the muscle mass of
the lower limbs was significantly reduced in the combina-
tion therapy subgroup. It is known that vitamin D receptors
are expressed in skeletal muscles, and activated vitamin D
Chan
ges in bone mineral densit
ey and m
uscle mass after 6 months of treatment be
tween combination of minodronate and acti
vated vitamin D therapy vs
group (n=60) and the minodronate-
alone subgroup (n=70).

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, alfalcaldol adminis
tration 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 sup
press 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 conse
quence 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 de
crease.

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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