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**Effect of alendronate on bone metabolic indices and bone mineral density
in patients treated with high-dose glucocorticoid: a prospective study**

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Conflicts of interest None

Mini-Abstract: This prospective study in the very early phase after initiation of glucocorticoid (GC) treatment showed that alendronate was effective in suppressing accelerated bone resorption and subsequent decrease in bone mineral density (BMD) at the lumbar spine of patients with high-dose GC treatment.

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Running title: Glucocorticoid therapy and alendronate

Abstract

Introduction How bisphosphonates affect bone metabolism and BMD of patients with high-dose GC in the early phase, especially within 1 month is unclear.

Methods We examined the prospective effects of daily 5mg alendronate on bone metabolism and BMD in 20 patients with high-dose GC (at least 40 mg prednisolone/day), and compared them to 34 high-dose GC-treated patients without alendronate. *Results* Serum levels of calcium decreased at day 28 in the alendronate group. Urinary calcium excretion significantly increased after day 7 in both groups. The increase in serum parathyroid hormone (PTH) level at day 7 in the control group was not observed in the alendronate group, but PTH levels increased at day 28 and month 3 in the alendronate group. As for the bone turnover markers, the serum osteocalcin level decreased in both alendronate and control groups but serum bone-type alkaline phosphatase levels did not show significant changes. Although the urinary type I collagen cross-linked N-telopeptides (NTX) level showed significant increases on days 7 and 28 in the control group, such early increases in urinary NTX were not observed in the

alendronate group. Thereafter, the urinary NTX levels fell slowly in the alendronate group significantly. BMD at the lumbar spine significantly decreased from month 1 in the control group, whereas in the alendronate group, BMD at the lumbar spine maintained almost the same level at all time points observed.

Conclusion Alendronate was effective in suppressing bone resorption and subsequent BMD decrease at the lumbar spine in patients with high-dose GC treatment.

Key words: Glucocorticoid, Alendronate, Osteoporosis, Bone metabolic indices, Bone mineral density, high-dose GC

Introduction

Glucocorticoids (GC) are widely used for the treatment of autoimmune, neurological, dermatological and respiratory diseases. GC-induced osteoporosis (GIO) is a serious problem for patients taking GC. GC causes bone loss and an increase in bone fragility, resulting in a great increase in fracture risk [1-6]. In particular, the relative risk of fracture increases by as much as 75 % within the first 3 months after initiation of GC therapy [4]. GC induces bone fragility by several mechanisms [7-12]. The negative effect of GC on bone formation is most crucial in the pathogenesis of GIO. Moreover, high-dose GC accelerated bone resorption occurs in the early phase. Bisphosphonates are one of the most effective agents for the reduction of osteoporotic fractures. Aminobisphosphonates, such as alendronate or risedronate, are clinically used for osteoporosis, and extensive evidence indicates apparent reduction of fracture risk by aminobisphosphonates. Those studies showed that aminobisphosphonates induced the large increase in bone mineral density (BMD) attributed by strong suppression of bone resorption in osteoporotic

patients [13-16]. In most reports, the effects of aminobisphosphonates were evident in any age, across genders and in patients with or without previous fractures [16-18]. Moreover, bisphosphonates were also effective in secondary osteoporosis, such as primary hyperparathyroidism, GIO and hypogonadism [19-26]. Alendronate is one of the first line drugs for the preservation and treatment of GIO with extensive evidence [19-22, 26]. In a randomized prospective clinical trial among patients with a rheumatic disease taking GC at a daily dose of at least 7.5 mg prednisolone, alendronate was more effective in the prevention of GC-induced bone loss than alfacalcidol [26]. Although the efficacy of alendronate in increasing BMD and reducing fracture risk in patients with low- or moderate-dose GC treatment has been well confirmed, there is little evidence about its effects in patients with high-dose GC treatment. High-dose prednisolone or intravenous pulse methylprednisolone is often used for the initial control of many rheumatic, hematologic and neurological diseases. Mok et al. recently reported that risedronate improved BMD at the lumbar spine in patients with high-dose GC (more than 0.5 mg/kg/day prednisolone) [27]. Moreover,

Okada et al. reported that alendronate protected premenopausal women from bone loss and fracture associated with high-dose GC therapy (1mg/kg/day prednisolone) [28]. However, the effects of bisphosphonate on bone metabolism and BMD of patients with high-dose GC treatment in the early phase, especially within 1 month are still unclear. Therefore, we prospectively investigated the effects of daily alendronate (5mg/day) on bone metabolism and BMD in 20 patients with high-dose GC (at least 40 mg/day prednisolone), and compared them to 34 high-dose GC-treated patients without alendronate.

Methods

Patients and study protocol

Fifty-four patients who were scheduled to start high-dose GC therapy (initial daily dose of 40 mg/day or more prednisolone) were enrolled in this study. Among them, 20 patients who started with 5 mg daily alendronate at the same time as GC treatment were assigned to the alendronate group. For the control group, 34 patients who received high-dose GC therapy were not treated with alendronate.

Control GC-treated patients were enrolled from March 2003 to May 2005 while the alendronate-treated group was enrolled from June 2005 to March 2008. They were consecutive patients and all patients were enrolled in the study. 11 and 6 patients were pre- and postmenopausal in the control group. 6 and 5 patients were pre- and postmenopausal in the alendronate group. All premenopausal patients were not amenorrheic, although serum estrogen levels of these patients were not measured. Fasting morning blood and urine samples were collected from the patients before initiation of treatment and on days 7 and 28 and months 3 and 6 of GC therapy. Serum levels of albumin, calcium (Ca), phosphorus, and creatinine (Cr), as well as urinary Ca and Cr were measured at each point. Biochemical markers of bone metabolism were also measured on the indicated days. Ca supplements and vitamin D were administered to all patients, but no other drugs that could influence bone metabolism were given. The underlying diseases were classified as collagen diseases (Control: n=14; Alendronate: n=10), hematopoietic diseases (Control: n=4; Alendronate: n=2), and neuroimmune diseases (Control: n=14; Alendronate: n=8). We excluded

subjects whose activities of daily living were diminishing on medical review and physical examination. All patients included in this study provided written informed consent for participation, and the study protocol was approved by the Institutional Review Board of each hospital.

Biochemical indices

As bone formation indices, serum osteocalcin (OCN) and bone-type alkaline phosphatase (BAP) were measured. OCN was determined in an immunoradiometric assay (BGP IRMA, Mitsubishi Chemical Medience Corporation, Japan, normal range: 2.5–13 ng/dL) and BAP was also measured in an enzyme immunoassay (Osteolinks BAP, DS-Pharma Biochemical Co. Ltd, JAPAN, normal range: 7.9–29.0 IU/L) [30]. As bone resorption markers, urinary levels of type I collagen cross-linked N-telopeptide (NTx) were measured in an enzyme immunoassay (Osteomark NTX, Mochida Pharmaceutical Co. Ltd, JAPAN, normal range: 9.3–54.3 nmol BCE/mmol Cr) [31]. Intact PTH was measured in an electrochemiluminescent immunoassay (Eclisys 2010 PTH,

Roche Diagnostics K.K, Japan, normal range: 5–65 pg/mL) [32].

BMD measurements

BMD values were measured by dual-energy X-ray absorptiometry using QDR-2000, QDR-4500SL, DELPHIQDR-4500C or XR-30 (Hologic Inc., Waltham, MA, USA) at the lumbar spine (L₂₋₄). BMD was automatically calculated from the bone area (cm²) and bone mineral content (BMC) (g), and expressed absolutely in g/cm². The coefficients of variation of measurements of the lumbar spine were 0.9 %. BMD was measured on day 0, and in months 3 and 6.

Statistical analysis

Statistical analysis of data was performed with the StatView ver.5.0 software package (SAS Institute Inc., Berkeley, CA, USA). The unpaired Student's *t*-test was used to compare differences in patient profiles in both groups. Changes in bone metabolic indices during GC therapy were assessed using the nonparametric Student's *t*-test. Results are presented as the mean ± SE, and

$p < 0.05$ was considered to indicate significance. The figures show data expressed as percent changes of the baseline value.

Results

Patient's baseline characteristics

Baseline clinical, densitometric and biochemical characteristics of the GC-treated patients in two groups were not statistically different except for their ages (Table 1). The age in the alendronate group was relatively younger than that in the control group ($p < 0.05$). All patients were treated with at least 40 mg/day prednisolone.

Biochemical Markers

The longitudinal changes in serum and urinary Ca levels as well as serum PTH levels in patients treated with high-dose GC are shown in figures. The serum Ca level showed significant increase only at day 28 in the control group ($p < 0.01$). Urinary Ca excretion increased on day 7 and continued to increase until 6

months of GC therapy in this group. PTH also showed an increase on day 7, and the level returned to the basal level within 3 months in the control group (Fig. 2). On the other hand, in the alendronate group, serum levels of Ca significantly decreased at day 28 ($p<0.01$), and this decreased level was maintained until month 3, then recovered as the basal level at month 6 (Fig. 1). Urinary excretion of Ca significantly increased after day 7 ($p<0.05$) in the alendronate group. As for the PTH level, an increase in serum PTH at day 7 observed in the control group was not observed in the alendronate group, but PTH levels continued to maintain the significantly higher level until month 3 ($p<0.01$, Fig. 2).

Effects of alendronate on bone metabolic indices

We examined the longitudinal change in bone metabolic indices in patients treated with high-dose GC. OCN and BAP are considered to be bone formation indices, particularly the former is a GC-sensitive marker. On the other hand, urinary NTX is considered to be a bone resorption index.

In the control group, the serum OCN level significantly decreased on day 7

($p < 0.01$) of GC administration, but then returned to the baseline after 3 months, while the serum BAP level did not change significantly during 6 months (Fig. 3). In the alendronate group, the serum OCN were significantly low levels for 3 months ($p < 0.01$) and then recovered to the basal value at month 6. On the other hand, serum BAP in the alendronate group did not change at each time measured. As for the bone resorption index, the urinary NTX level showed significant increases on days 7 ($p < 0.01$) and 28 ($p < 0.05$), and thereafter fell to the basal level at month 6 in the control group (Fig. 4). In the alendronate group, the urinary NTx level minimally increased at day 7, then these levels significantly fell under the basal data on months 3 and 6 ($p < 0.05$).

Effects of alendronate on BMD

The longitudinal changes in BMD at the lumbar spine in patients treated with high-dose GC are shown in Fig. 5. BMD at the lumbar spine significantly decreased at month 1 ($p < 0.05$) in the control group, and thereafter continued to decrease until month 6 ($P < 0.01$). In the alendronate group, BMD did not change

significantly at all time points observed.

Discussion

In the present study, we investigated the effects of alendronate on bone metabolism and BMD among patients treated with high-dose GC in early stage.

The urinary Ca excretion increased after the start of high-dose GC therapy and moreover PTH increased on days 7 and 28 of GC therapy in the control group. These data were compatible with our previous reports [33]. We speculated that an early transient increase in serum PTH level was due to direct stimulation of the parathyroids by GC as previously described [33].

Such an increase of urinary Ca excretion was observed not only in the control group but also in the alendronate group. Under normal condition, blood Ca level is decreased through induced apoptosis of osteoclasts with alendronate and subsequent suppression of osteoclastic bone resorption, resulting in decreasing urinary excretion of Ca. On the other hand, high-dose GC treatment is known to suppress resorption of Ca from renal tubules and accelerate excretion of Ca.

Therefore increasing urinary excretion of Ca in the alendronate group would suggest that alendronate did not affect on the Ca resorption from renal tubules.

In the alendronate group, no early increase in the serum PTH level was observed. This would suggest that alendronate directly suppressed PTH secretion with some action on the parathyroids, though its mechanism of action is unknown.

In the control group, serum OCN levels decreased at days 7 and 28, and then seemed to recover in months 3 and 6, although serum BAP levels slightly fell at day 28. On the other hand, serum OCN levels in the alendronate group did not recover in months 3 and 6. They were still lower levels, the same as those of days 7 and 28. This suggested that alendronate did not modulate early changes in the bone formation by high-dose GC, although alendronate seemed to reduce bone formation indices, especially serum OCN levels, in months 3 and 6. This long-term suppression of bone formation in the alendronate group will be attributed to suppressed bone resorption and subsequent inhibition of bone formation.

In the control group, urinary NTX levels increased in the early phase after initiation of GC therapy (on days 7 and 28) as shown in our previous report [33]. This result suggests that high-dose GC will increase PTH secretion directly in the early phase of the GC therapy and subsequently stimulate bone resorption. Though it is well known that alendronate treatment reduces the bone resorption marker after 1 month of administration, in the present study, urinary NTX level at day 28 was almost the same level as that at the baseline in the alendronate group. This result suggests that alendronate partially suppress the stimulated bone resorption by high-dose GC therapy. These findings would indicate that the dosage of alendronate was not sufficient to suppress bone resorption stimulated by high dose-GC completely.

In the present study, BMD at the lumbar spine in the control group significantly decreased within one month after initiation of high-dose GC therapy. The BMD continued to decrease during 6 months in the control group. On the other hand, BMD at the lumbar spine in the alendronate group did not alter from the background level. This suggests that alendronate effectively prevented bone

loss attributed with high-dose GC treatment, which was compatible with previous studies [4, 28, 34, 35]. Since the dose of GC usually is reduced from high dose to the moderate in 3 months, these results suggest that bone fragility might be affected from the early stage of high-dose GC therapy and that the higher fracture risk will remain during the high-dose GC therapy without alendronate treatment. The treatment with 5 mg alendronate might sufficiently suppress the catabolic effects of moderate- or low-dose GC on bone and only partly preserve high-dose GC-induced osteopenia. In addition, several months might be required for alendronate to improve effectively their bone loss induced by high-dose GC therapy.

In the present study, there are several limitations to estimate the efficacy of 5mg alendronate treatment on bone loss induced by high-dose GC therapy. First, the sample size was not large enough to reach definitive conclusions. Moreover, there were some differences in age in control and alendronate groups, although previous studies indicate that age was not significantly related to BMD increase at the lumbar spine by bisphosphonate treatment [16, 18]. However, we cannot

rule out the possibility that age affected GC-induced changes of bone metabolism and BMD in both groups. Moreover, estrogen state might modulate them, since the proportion of premenopausal patients were a little higher in the alendronate group, compared to that in the control group. Additionally, alendronate did not alter the high-dose GC effect on bone in early phase after the initiation of GC therapy in spite of no significant BMD change during treatment with alendronate. A previous study indicated that BMD changes were correlated to urinary NTX changes in alendronate-treated patients with GC treatment [35], suggesting that pre-treatment with alendronate or its higher dose administration might be more effective to suppress GC-induced fractures satisfactorily in early stage, since vertebral fractures induced by GC are frequent early after the initiation of high-dose GC therapy in patients treated with high-dose GC. Further study will be required to clarify these issues.

In conclusion, alendronate effectively suppressed bone resorption and the subsequent BMD decrease at the lumbar spine in patients with high-dose GC treatment.

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Figure Legends

Fig. 1. Effects of alendronate on serum and urinary Ca levels

Serum Ca levels and urinary Ca excretion were followed at the indicated time for 6 months in patients with high-dose GC treatment. * $p < 0.05$, ** $p < 0.01$

Fig. 2. Effects of alendronate on serum levels of PTH

Serum PTH levels were followed at the indicated time for 6 months in patients with high-dose GC treatment. * $p < 0.05$, ** $p < 0.01$

Fig. 3. Effect of alendronate on bone formation indices

Serum levels of OCN and BAP were followed at the indicated time for 6 months in patients with high-dose GC treatment. * $p < 0.05$, ** $p < 0.01$

Fig. 4. Effects of alendronate on bone resorption index

Urinary NTX levels were followed at the indicated time for 6 months in patients with high-dose GC treatment. * $p < 0.05$, ** $p < 0.01$

Fig. 5. Effects of alendronate on BMD at the lumbar spine

BMD at the lumbar spine were followed at the indicated time for 6 months in patients with high-dose GC treatment. * $p < 0.05$, ** $p < 0.01$

Table. 1 Baseline data of high dose GC-treated patients

	Alendronate	Control
<i>No. of Patients</i>	20	34
<i>Age</i>	46.9±16.8 *	58.4±17.5
<i>M : F</i>	9 : 11	15 : 19
<i>OCN (ng/ml)</i>	4.1±3.4	3.9±2.2
<i>BAP (U/l)</i>	18.4±12.1	24.7±12.0
<i>u NTx (nm/mmcrl)</i>	57.1±37.8	62.3±50.6
<i>PTH (pg/ml)</i>	32.8±13.8	36.2±25.6
<i>u Ca/Cr</i>	0.15±0.15	0.13±0.11
<i>BMD(g/cm²)</i>		
<i>Lumbal Spine(L2-4)</i>	0.91±0.13	0.94±0.15
<i>Femoral Neck</i>	0.72±0.11	0.74±0.14

* : P<0.05, compared to control group

Figure. 1

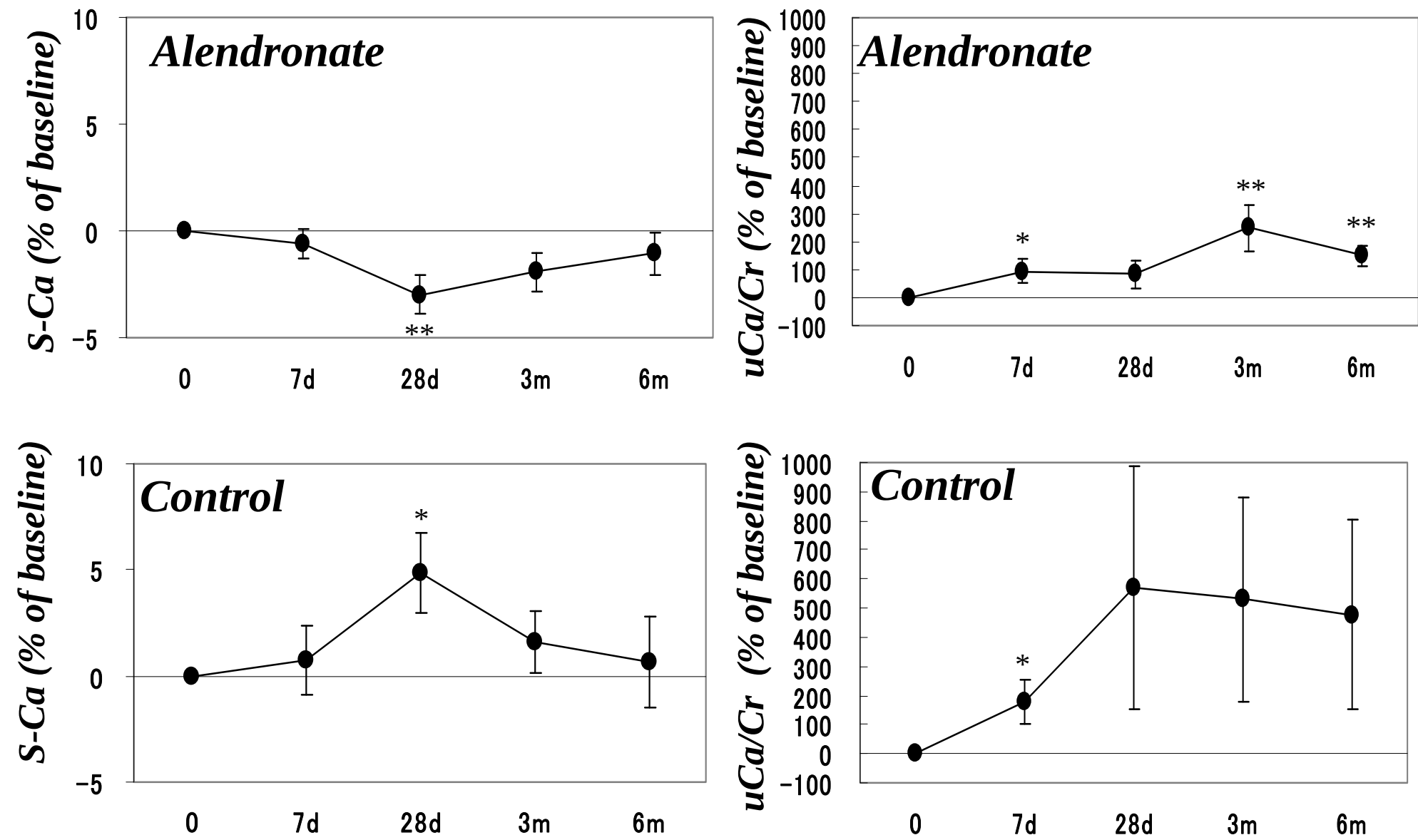


Figure. 2

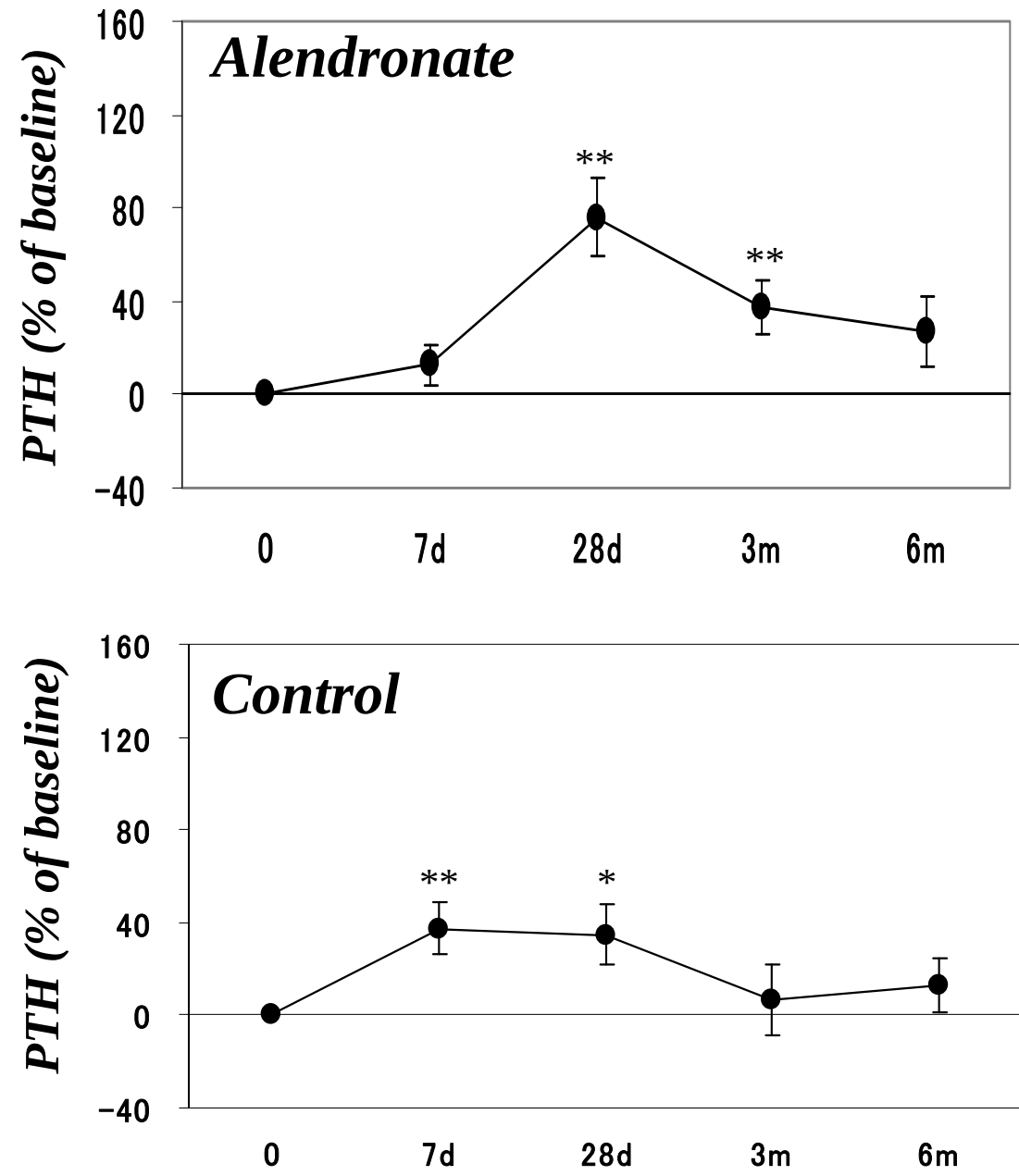
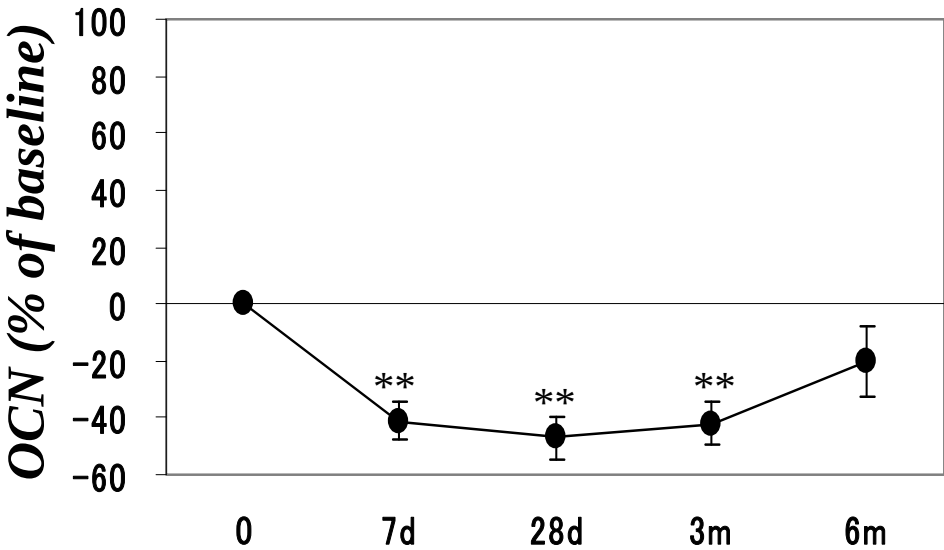
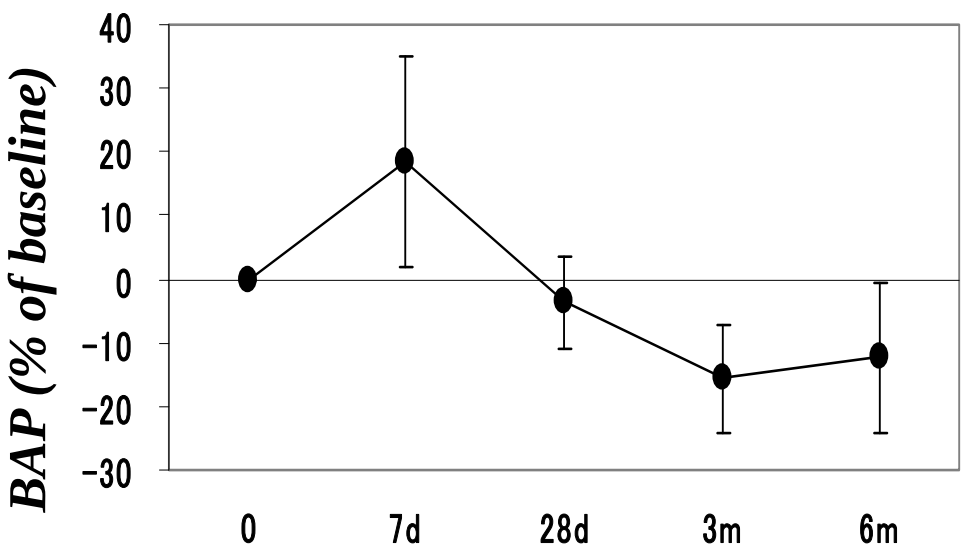


Figure. 3

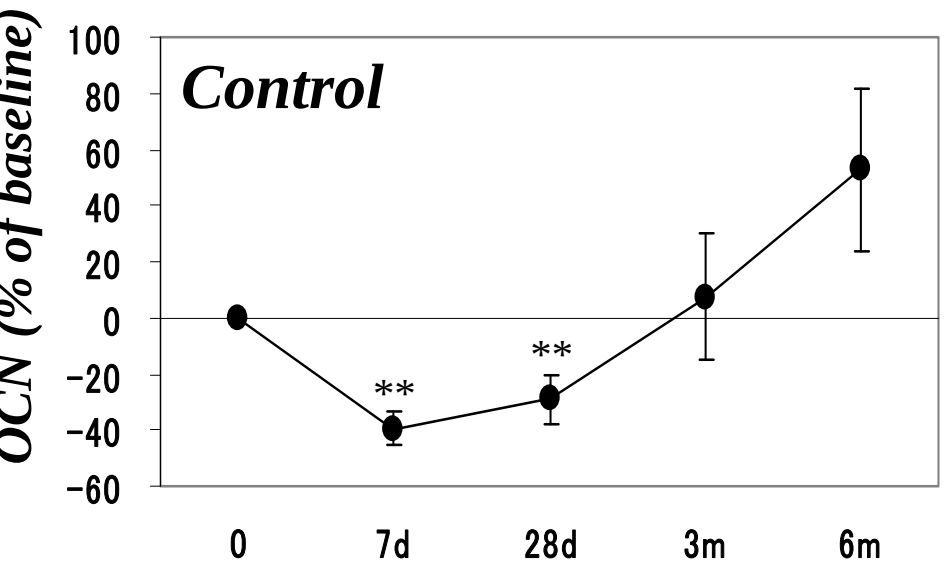
Alendronate



Alendronate



Control



Control

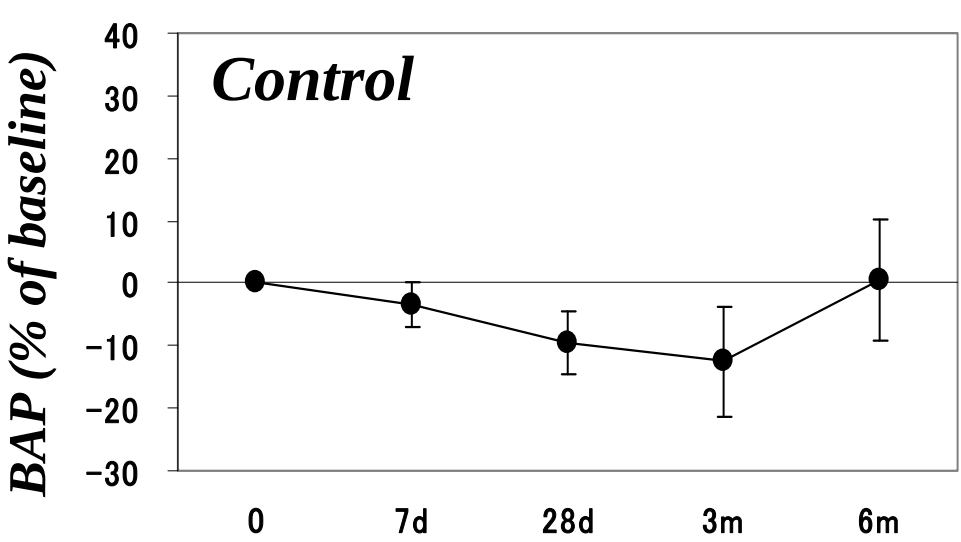


Figure. 4

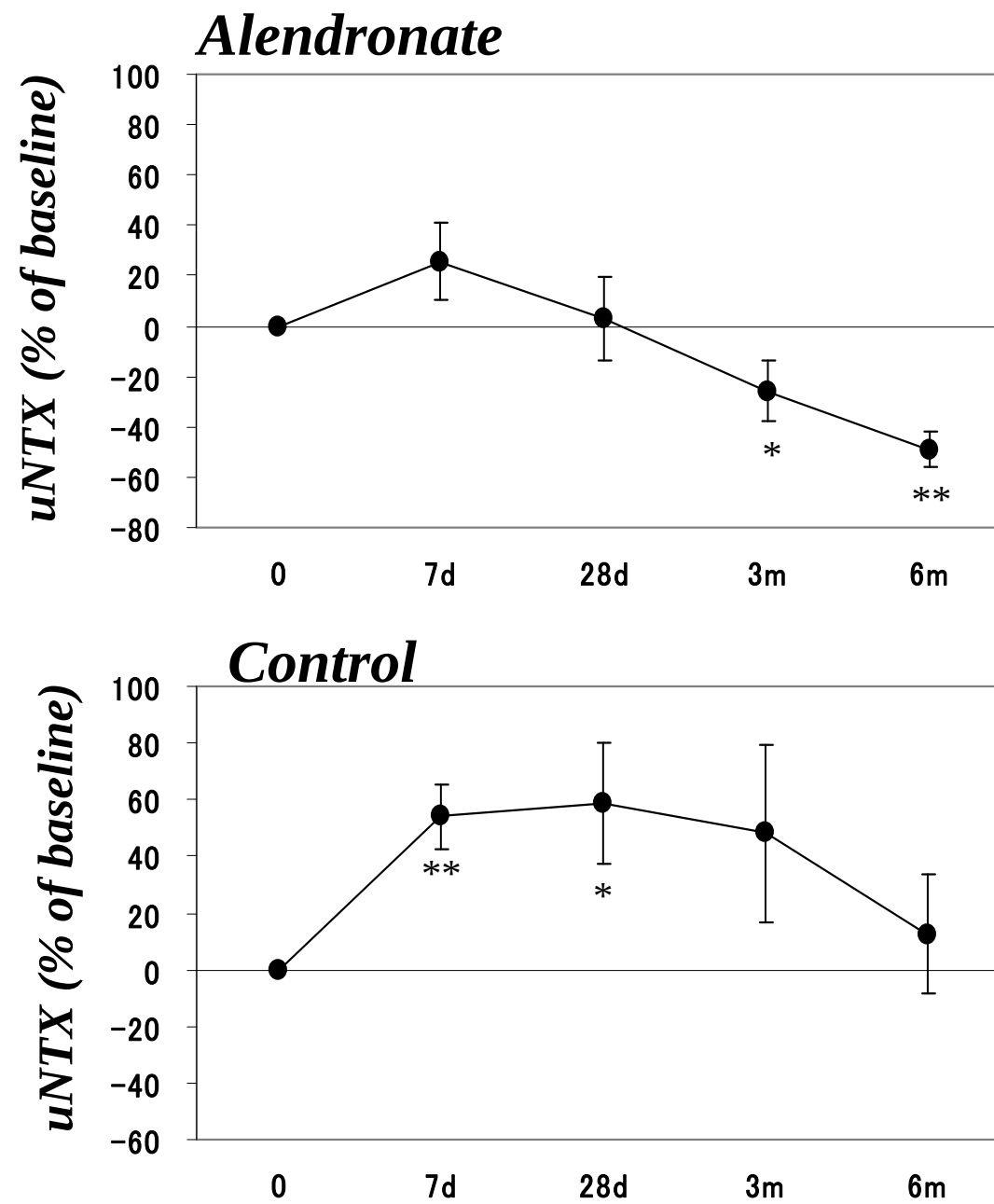


Figure. 5

