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ORIGINAL RESEARCH

Influence of treatment with alendronate on the speed of sound, an ultrasound parameter, of the calcaneus in postmenopausal Japanese women with osteoporosis: a clinical practice-based observational study

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Purpose: The influence of alendronate (ALN) treatment on the quantitative ultrasound parameters of the calcaneus remains to be established in Japanese patients. The aim of the present clinical practice-based observational study was to examine the influence of ALN treatment for 1 year on the speed of sound (SOS) of the calcaneus and bone turnover markers in postmenopausal Japanese women with osteoporosis.

Patients and methods: Forty-five postmenopausal Japanese women with osteoporosis who had received treatment with ALN for more than 1 year were enrolled in the study. The SOS and bone turnover markers were monitored over 1 year of ALN treatment.

Results: The urinary levels of cross-linked N-terminal telopeptides of type I collagen and serum levels of alkaline phosphatase decreased significantly from the baseline values (−44.9% at 3 months and −22.2% at 12 months, respectively). The SOS increased modestly, but significantly, from the baseline value (0.6% at both 6 and 12 months). The percentage decrease in the urinary levels of cross-linked N-terminal telopeptides of type I collagen at 3 months was significantly correlated with the percentage increase in the SOS only at 6 months (correlation coefficient, 0.299).

Conclusion: The present study confirmed that ALN treatment suppressed bone turnover, producing a clinically significant increase in the SOS of the calcaneus in postmenopausal Japanese women with osteoporosis.

Keywords: postmenopausal osteoporosis, quantitative ultrasound (QUS), SOS, bone turnover, biochemical markers

Introduction

Osteoporosis most commonly affects postmenopausal women, placing them at significant risk for sustaining fractures. Alendronate (ALN) is widely used as a first-line drug for the treatment of postmenopausal osteoporosis because of its established efficacy, according to the Fracture Intervention Trial and a recent systematic review of eleven randomized controlled trials (RCTs), against vertebral, nonvertebral, hip, and wrist fractures.[1–3]

Because ALN treatment increases bone mineral density (BMD) at the lumbar spine, femoral neck, and total hip in postmenopausal women with osteoporosis – as reported in the aforementioned Fracture Intervention Trial[1,2] – the BMD measured by dual-energy

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X-ray absorptiometry (DXA) remains the optimal method for monitoring the response to ALN treatment. Quantitative ultrasound (QUS) is a more recently developed noninvasive method to study the bone density and structure in vivo. QUS parameters (speed of sound [SOS], broadband ultrasound attenuation [BUA], and stiffness index [SI]) can predict the risk of development of hip, wrist, and total nonvertebral fractures over a period of up to 10 years.[4] It may be possible to better account for structural changes of the bone by means of QUS than by the traditional DXA method.[5] Gonnelli et al[6] reported that ALN treatment increased the QUS parameters at the calcaneus in postmenopausal women with osteoporosis (at 1 year, SOS: 0.4%, BUA: 1.1%, and SI: 3.2%; at 4 years, SOS: 1.2%, BUA: 1.9%, and SI: 9.0%). Thus, QUS of the calcaneus can be a useful tool for monitoring the response to ALN treatment.

RCTs in postmenopausal women with osteoporosis in Japan have indicated that short-term (1–3 years) ALN treatment suppresses bone turnover, increases BMD, and reduces the incidence of vertebral fractures.[7–10] However, the effect of ALN treatment on the QUS parameters remains to be established in Japanese patients. The SOS at the calcaneus can be measured using a QUS device (CM-200; Elk Corp., Osaka, Japan). The authors hypothesized that ALN treatment would produce an increase of the SOS at the calcaneus in Japanese patients similar to the increase produced in Caucasian patients. The aim of the present clinical practice-based observational study was to examine the influence of 1 year's ALN treatment on the SOS and on bone turnover markers in postmenopausal Japanese women with osteoporosis.

Material and methods
Subjects

Forty-five postmenopausal Japanese women with osteoporosis who had been treated with ALN (35 mg weekly) for more than 1 year at the outpatient clinic of Hiyoshi Medical Clinic (Kanagawa, Japan) were identified during the 6-month period between October 1, 2011, and March 31, 2012, and were retrospectively analyzed. The 35 mg weekly dose indicated is the dose used in Japan for the treatment of osteoporosis in postmenopausal women and has been recognized as being safe and effective.[7–10] All of women identified had been estrogen or bisphosphonate naïve. They had started ALN treatment during the 18-month period between October 1, 2009, and March 31, 2011, and had been continuing the treatment for more than 1 year at the authors' outpatient clinic. The inclusion criterion prior to ALN treatment was postmenopausal osteoporosis according to the Japanese diagnostic

criteria[11,12] – namely, patients with (1) a BMD < 70% of the young adult mean (YAM) or "present" osteopenia on X-ray images of the spine or (2) a BMD of 70%–80% of the YAM or "possible" osteopenia on X-ray images of the spine along with a history of osteoporotic fractures. Because spine DXA is considered as a useful monitoring method for osteoporosis in Japanese women, and because QUS appears to be less useful,[13] the diagnosis of osteoporosis was undertaken using both the SOS (<70% of the YAM or 70%–80% of the YAM along with a history of osteoporotic fractures) and the X-ray findings of the spine ("present" osteopenia or "possible" osteopenia along with a history of osteoporotic fractures). The exclusion criterion was a history of reflux esophagitis, gastric or duodenal ulcer, gastrectomy, renal failure, or bone diseases, including cancer-induced bone loss because of aromatase inhibitors, primary hyperparathyroidism, hyperthyroidism, Cushing's syndrome, multiple myeloma, Paget's disease of the bone, rheumatoid arthritis, and osteogenesis imperfecta. None of the patients received elementary calcium or natural vitamin D supplementation, although they were instructed with the aid of brochures to achieve daily intakes of 800 mg of calcium and 800 IU of vitamin D through food consumption.

The assessment performed prior to the start of the ALN treatment included a medical history, physical examination, plain radiography of the thoracic and lumbar spine, measurement of the SOS of the calcaneus, and blood and urinary biochemical tests – including serum calcium, phosphorus, and alkaline phosphatase (ALP) – and urinary cross-linked N-terminal telopeptides of type I collagen (NTX). The urinary NTX levels were measured at 3 months after the start of treatment. The serum levels of calcium, phosphorus, and ALP and the SOS of the calcaneus were measured every 6 months after the start of treatment. Plain X-rays of the thoracic and lumbar spine were taken after 1 year of treatment. The outcome of ALN treatment for 1 year was evaluated.

Assessment of morphometric vertebral fractures

Plain lateral X-ray films of the thoracic and lumbar spine were obtained at the baseline to detect evidence of morphometric vertebral fractures. According to the Japanese criteria, a vertebral fracture is defined according to the vertebral height on lateral X-ray films.[11,12] Briefly, the vertebral height is measured at the anterior (A), central (C), and posterior (P) parts of the vertebral body, and the presence of a vertebral fracture is confirmed when (1) a reduction in the vertebral height of more than 20% (A, C, and P) as compared with the height of

the adjacent vertebrae is observed, (2) the C/A or C/P ratio is <0.8, or (3) the A/P ratio was <0.75. The assessment for vertebral fractures was performed at the T4–L4 level.

Assessment of clinical vertebral and nonvertebral fractures

Low-trauma osteoporotic clinical fractures were assessed. Clinical vertebral fractures were determined based on the clinical symptoms and findings of radiographies or magnetic resonance images of the lumbar and thoracic spine. Nonvertebral fractures in terms of major osteoporotic fractures at the distal radius, proximal humerus, and hip were determined based on the clinical symptoms and radiographic findings of the wrist, shoulder, and hip joints, respectively.

Measurement of serum calcium, phosphorus, ALP, and urinary NTX

Serum and urine samples obtained from each patient were sent to Kotobiken Medical Laboratories, Inc (Yokohama, Kanagawa, Japan) for biochemical analyses. The serum calcium and phosphorus levels were measured using the standard laboratory techniques. The serum ALP levels were measured using the Japan Society of Clinical Chemistry reference method. The coefficient of variation ($CV = 100 \times$ standard deviation/mean) of two consecutive measurements within a day was <1.15% among 20 persons. The CV of two measurements at the same time point on 2 consecutive days was <4.08% among six persons. The urinary NTX levels were measured using an enzyme-linked immunosorbent assay. The CV of two consecutive measurements within a day was <7.4% among ten persons. The CV of two measurements at the same time point on 2 consecutive days was <15.0% among 24 persons.

Measurement of SOS of the calcaneus

The SOS of the left calcaneus was measured using a QUS device (CM-200; Elk Corporation, Osaka, Japan). Both the reliability and the reproducibility of this QUS device have been reported as follows: the CV using the phantom technique was 0.15%, and that in vivo was 0.27%.[14]

Statistical analysis

The data are expressed in the tables and figures as mean plus or minus standard deviation. A one-way analysis of variance (ANOVA) with repeated measurements was used to determine the significance of the longitudinal changes in the SOS and biochemical markers. A single regression analysis was used to examine correlations between change in the urinary NTX at 3 months and changes in the SOS at 6 and 12 months. All the statistical analyses were performed using statistical software (StatView-J5.0 for Windows; SAS Institute Inc, Cary, NC). A significance level of $P < 0.05$ was used for all the comparisons.

Results
Characteristics of study subjects at start of treatment

Table 1 shows the anthropometric characteristics of the study subjects at the start of the ALN treatment. The mean age of the subjects was 69.0 years (range, 47–92 years). Table 2 shows the SOS and biochemical markers at the start of ALN treatment. The mean SOS was 1465 m/s, which corresponds to 64.1% of the YAM. The mean serum calcium, phosphorus, and ALP levels were 9.2 mg/dL, 3.4 mg/dL, and 259 IU/L, respectively, all being within the respective normal ranges (8.4–10.2 mg/dL, 2.5–4.5 mg/dL, and 100–340 IU/L, respectively). However, the mean urinary NTX level was 61.7 nmol bone collagen equivalent (BCE)/mmol creatinine (Cr), which was higher than the normal range for Japanese women (9.3–54.3 nM BCE/mM Cr),[15] indicating a high bone turnover, characteristic of osteoporosis.

Changes in SOS of the calcaneus

Figure 1 shows the changes in the SOS of the calcaneus. A one-way ANOVA with repeated measurements showed a significant longitudinal increase in the SOS for 1 year ($P < 0.0001$). The mean rates of change in the SOS after 6 and 12 months of treatment were both 0.6% (Table 3).

Changes in biochemical markers

Figure 2 shows the changes in the biochemical markers. The mean urinary NTX levels decreased to the normal range for Japanese women (9.3–54.3 nmol BCE/mmol Cr)[15] after 3 months of treatment, and the mean serum ALP levels decreased and remained within the normal range (135–340 IU/L) during the 1-year treatment period. A one-way ANOVA with repeated measurements showed

Table 1 Baseline anthropometric characteristics of study subjects

Anthropometric characteristic	Mean ± SD	Range
Age (years)	69.0 ± 9.1	47–92
Height (m)	1.54 ± 0.06	1.41–1.70
Body weight (kg)	52.5 ± 8.0	35–80
Body mass index (kg/m²)	22.0 ± 3.3	15.8–35.1

Abbreviation: SD, standard deviation.

Table 2 Baseline speed of sound (SOS) and biochemical markers

Variable	Mean ± SD	Range
SOS (m/s)	1465 ± 14	1433–1498
%YAM in SOS (%)	64.1 ± 6.4	49–79
Calcium (mg/dL)	9.2 ± 0.3	8.6–10.0
Phosphorus (mg/dL)	3.4 ± 0.5	1.6–4.1
ALP (IU/L)	259 ± 72	132–439
Urinary NTX (nM BCE/mM Cr)	61.7 ± 25.8	19.9–126.3

Notes: Normal ranges of serum calcium, phosphorus, and ALP were 8.4–10.2 mg/dL, 2.5–4.5 mg/dL, and 100–340 IU/L, respectively; standard range of urinary NTX was 9.3–54.3 nM BCE/mM Cr, and cutoff values of bone loss and vertebral fracture risk were 35.3 and 54.3 nM BCE/mM Cr, respectively.
Abbreviations: %YAM, percentage of young adult mean; ALP, alkaline phosphatase; BCE, bone collagen equivalent; Cr, creatinine; NTX, cross-linked N-terminal telopeptides of type I collagen; SD, standard deviation.

significant longitudinal decreases in the serum ALP and urinary NTX levels (both $P < 0.0001$). No significant longitudinal changes in the serum calcium or phosphorus levels were observed. The mean rate of change of the urinary NTX level after 3 months of treatment was −44.9% (Table 3). The mean rates of change in the serum ALP levels after 6 and 12 months of treatment were −19.7% and −22.2%, respectively (Table 3).

Correlations between changes in urinary NTX and changes in SOS of the calcaneus

A single regression analysis showed that the percent decrease in the urinary NTX at 3 months was significantly correlated with the percentage increase in the SOS only at 6 months (correlation coefficient, 0.299; $P < 0.05$).
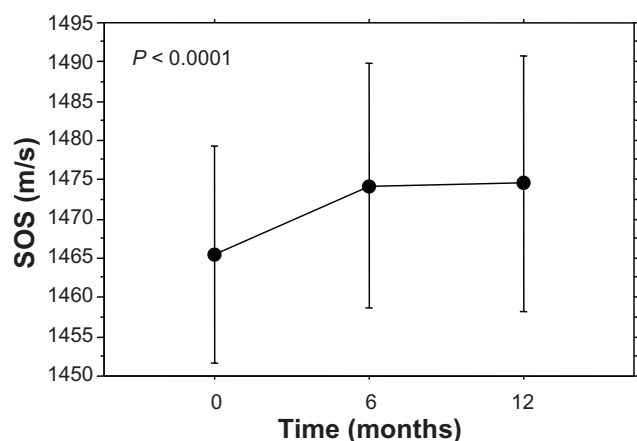
Figure I Changes in speed of sound (SOS).
Notes: Data are expressed as mean plus or minus standard deviation; the longitudinal changes in the SOS were analyzed using a one-way analysis of variance with repeated measurements; the longitudinal changes in the SOS were statistically significant ($P < 0.0001$).

Table 3 Percentage changes in speed of sound (SOS) and biochemical markers

Variable	3 months	6 months	12 months
SOS		0.6 ± 1.0	0.6 ± 1.0
Calcium		−1.2 ± 4.1	−0.7 ± 5.1
Phosphorus		−1.2 ± 13.8	2.6 ± 13.6
ALP		−19.7 ± 18.2	−22.2 ± 20.2
Urinary NTX	−44.9 ± 27.1		

Note: Data are expressed as mean plus or minus standard deviation.
Abbreviations: ALP, alkaline phosphatase; NTX, cross-linked N-terminal telopeptides of type I collagen.

Incident fractures

During the 1-year treatment period, one patient experienced a proximal humerus fracture. None of the other patients experienced morphometric or clinical vertebral fractures.

Side effects

One patient experienced stomach pain and one patient complained of thirst after the start of ALN treatment, but these symptoms were transient. Three patients underwent a tooth extraction during the 1-year treatment period with ALN. No serious adverse events, including osteonecrosis of the jaw, femoral diaphysis atypical fractures, or atrial fibrillation,[16–18] were observed.

Discussion

The present study confirmed that ALN treatment decreased the urinary NTX and serum ALP levels (−44.9% at 3 months and −22.2% at 12 months, respectively), producing a modest but significant increase in the SOS of the calcaneus (0.6% at both 6 and 12 months) in postmenopausal Japanese women with osteoporosis. The discussion points to be focused on were (1) whether the decreases in the bone turnover markers would be similar to those reported from the authors' previous studies, (2) whether the increase in the SOS of the calcaneus would be significant and greater than the range of reproducibility, and (3) whether the early changes in the urinary NTX might predict later changes in the SOS of the calcaneus.

The urinary NTX levels were measured at 3 months after the start of the ALN treatment. Measuring the urinary NTX levels at this time after the start of ALN treatment provides important information and is sufficient to monitor the effects of treatment of osteoporosis.[19] The authors' previous clinical practice-based observational studies showed that ALN treatment decreased the urinary NTX (by about −45% at 3 months) and serum ALP (by about −21.0% at 1 year) in postmenopausal Japanese women with osteoporosis,[20–23] which is consistent with the results of previous RCTs.[8,10]
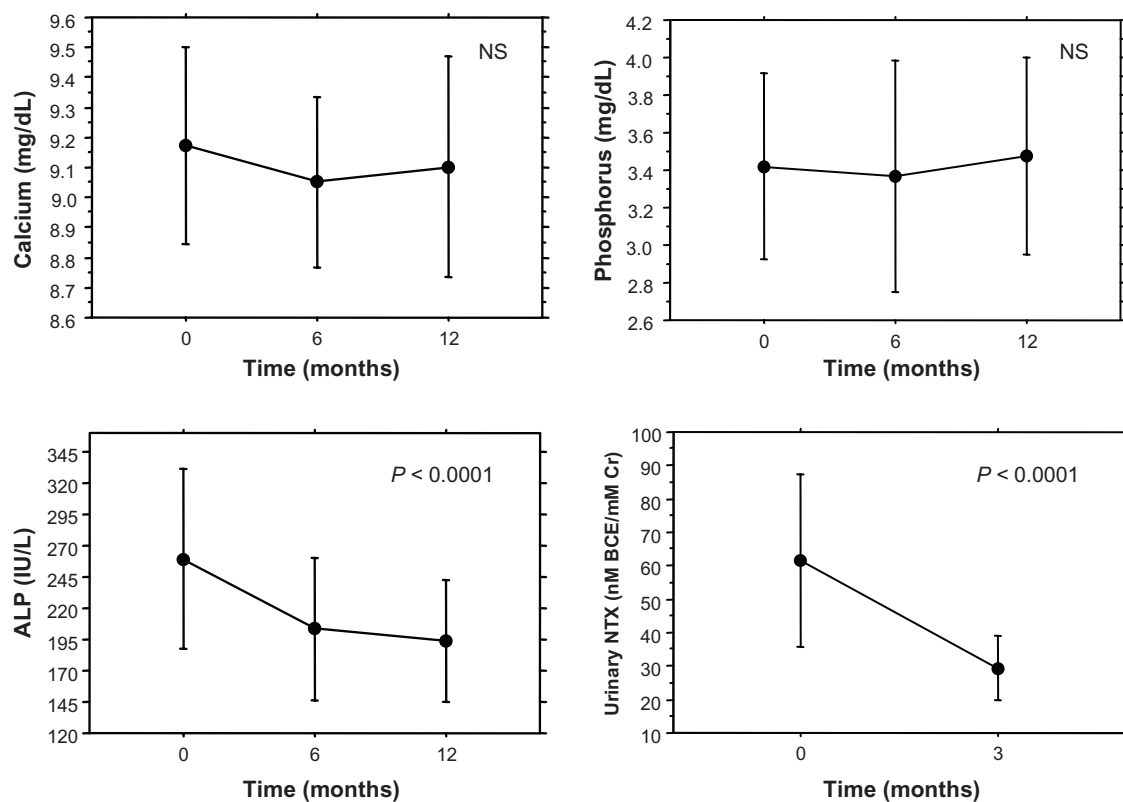
Figure 2 Changes in biochemical markers.
Notes: Data are expressed as mean plus or minus standard deviation; the longitudinal changes in biochemical markers were analyzed using a one-way analysis of variance with repeated measurements; the longitudinal changes in the serum ALP and urinary NTX were statistically significant (both $P < 0.0001$).
Abbreviations: ALP, alkaline phosphatase; BCE, bone collagen equivalent; Cr, creatinine; NS, not significant; NTX, cross-linked N-terminal telopeptides of type I collagen.

The reductions in the urinary NTX and serum ALP levels in the present study were comparable with those reported from previous studies. Clinical practice-based observational studies confirmed that ALN treatment for 1 year successfully suppressed bone turnover in postmenopausal Japanese women with osteoporosis.

The mean age of the study subjects at the start of the ALN treatment was 69.0 years. The reference values of the SOS of the calcaneus in healthy Japanese women are 1487 m/s for those aged 65–69 years and 1481 m/s for those aged 70–74 years.[24] ALN treatment for 1 year increased the SOS of the calcaneus (1465 m/s at baseline, 1474 m/s at 6 months, and 1475 m/s at 12 months). Therefore, it was considered that ALN treatment might be useful for increasing the SOS of the calcaneus in postmenopausal Japanese women with osteoporosis. The rates of increase of the SOS were 0.6% at both 6 and 12 months, similar to the rates of increase reported in postmenopausal Caucasian women with osteoporosis (0.4% at 1 year).[6] Because the CV in vivo for the measurement of the SOS of the calcaneus was 0.27%,[14] the increase in the SOS of the calcaneus in the present study might be clinically significant.

The percentage decrease in the urinary NTX at 3 months was significantly correlated with the percentage increase in the SOS only at 6 months (correlation coefficient, 0.299). ALN treatment rapidly decreased the urinary NTX level up to 3 months, with the values maintained thereafter.[10] The early changes in the urinary NTX may be the key in patients treated with ALN. The results of the present study suggest that early changes in the urinary NTX after the start of ALN treatment may be predictive of an increase in the SOS of the calcaneus. However, the percentage decrease in the urinary NTX at 3 months was not significantly correlated with the percentage increase in the SOS at 12 months, probably because the SOS of the calcaneus may also have been significantly affected by various other factors, including lifestyle and seasonal variations, during the 1-year treatment period with ALN.[25–27]

The authors' previous study found that early changes in the urinary NTX were correlated with the 1-year response to the lumbar spine BMD to ALN treatment in postmenopausal Japanese women with osteoporosis.[19] Conversely, Kaji et al[28] reported that BMD increase at the lumbar spine after bisphosphonate treatment was not related to any pretreatment

parameters – including body size, body composition, and bone/mineral metabolism – in postmenopausal Japanese women with osteoporosis. Subsequently, the correlation between decreases in bone turnover markers and increases in bone mass parameters after ALN treatment remains controversial. Thus, further studies conducted on a large number of Japanese patients are needed to address this issue.

A 3-year RCT in postmenopausal Japanese women with osteoporosis showed that the incidence of morphometric vertebral fractures was 7.8% for the ALN group without patients receiving elementary calcium or natural vitamin D supplementation.[8] However, in the present study none of the subjects experienced morphometric vertebral fractures, despite comparable changes in the bone turnover markers and SOS after 1-year ALN treatment.[6,8,10] The lower incidence of morphometric vertebral fractures in the present study may be attributable to a lower proportion of frail patients with a higher risk of incident fractures at baseline, since osteoporosis was not diagnosed precisely using the BMD measured by DXA.

There are notable limitations of the present study. Importantly, the statistical quality of the present analyses may be relatively poor, because of the small sample size, the absence of a statistical power for the fracture incidence, and the retrospective nature of the analyses. Further studies are needed to reconfirm the authors' results.

Conclusion

The present study confirmed that ALN treatment suppresses bone turnover, producing a clinically significant increase in the SOS of the calcaneus in postmenopausal Japanese women with osteoporosis.

Disclosure

The authors report no funding sources or conflicts of interest in this work.

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