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Original Article

Effect of minodronate on the speed of sound of the calcaneus in postmenopausal women with an increased risk of fractures: A clinical practice-based observational study

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Abstract

Background: We previously reported that alendronate and risedronate reduce the urinary levels of cross-linked N-terminal telopeptides of type I collagen (NTX) by 44.9% and 34.7%, respectively, at 3 months after the start of treatment, and increase the speed of sound (SOS) of the calcaneus by 0.6% and 0.65%, respectively, at 12 months after the start of treatment in postmenopausal women with osteoporosis. The aim of the present clinical practice-based observational study was to examine the effect of treatment with minodronate for 12 months on the SOS of the calcaneus and on bone turnover markers in postmenopausal women with an increased risk of fractures.
Methods: Forty-two postmenopausal women with osteoporosis or osteopenia with a clinical risk factor for fractures who had been treated with minodronate for > 12 months were enrolled in the study. The SOS and bone turnover markers were monitored during treatment with minodronate for 12 months.
Results: Compared to their baseline values, the urinary levels of NTX at 3 months and the serum levels of alkaline phosphatase at 12 months were significantly decreased at 47.5% and 25.8%, respectively. At 12 months, the SOS increased modestly, but significantly, by 0.47%, compared to the baseline value.
Conclusion: The present study confirmed that minodronate suppressed bone turnover and modestly increased the SOS of the calcaneus in postmenopausal women with an increased risk of fractures.

Keywords: bone turnover; minodronate; postmenopausal women; quantitative ultrasound; speed of sound

1. Introduction

Osteoporosis mostly affects postmenopausal women and substantially increases the risk of bone fracture. Oral bisphosphonates such as alendronate and risedronate are widely used as first-line drugs for the treatment of postmenopausal osteoporosis. Oral minodronate, a nitrogen-containing bisphosphonate, was developed in Japan. A randomized, placebo-controlled, double-blind study demonstrated that 1 mg of minodronate daily for 2 years reduced the risk of vertebral fractures by 59% in postmenopausal women with established osteoporosis.[1] A recent randomized controlled trial (RCT) showed that 50 mg of monthly minodronate had a similar efficacy as 1 mg daily dose of minodronate in terms of the bone mineral density (BMD) of the lumbar spine and bone turnover markers with a similar tolerability in patients with involutional osteoporosis.[2] In Japan, monthly minodronate is the first-line drug for treating postmenopausal osteoporosis

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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because of the preference of patients and the convenience of a monthly dosing regimen, compared to a weekly dosing regimen.[3]

Minodronate increases the BMD of the lumbar spine and total hip in patients with involutional osteoporosis[2]; therefore, using dual-energy X-ray absorptiometry (DXA) to measure the BMD remains the optimal method for monitoring the response to minodronate treatment. Quantitative ultrasound (QUS) is a more recently developed noninvasive method to determine bone density and structure *in vivo*. Quantitative ultrasound parameters such as speed of sound (SOS), broadband ultrasound attenuation, and stiffness index can predict the risk of hip, wrist, and total nonvertebral fractures up to 10 years later.[4] Quantitative ultrasound may also provide a better assessment of the structural changes of bone, compared to DXA.[5]

The SOS of the calcaneus can be measured using a QUS device (CM-200; Elk Corp., Osaka, Japan). We recently reported the effects of 12 months of treatment with alendronate and risedronate on the SOS and on bone turnover markers in Japanese postmenopausal women with osteoporosis.[6,7] Alendronate and risedronate reduced the urinary levels of cross-linked N-terminal telopeptides of type I collagen (NTX) and the serum levels of alkaline phosphatase (ALP), and modestly increased the SOS. To date, however, very few studies have examined the effects of minodronate on the SOS in postmenopausal women with osteoporosis. The aim of the present clinical practice-based observational study was to examine the effects of 12 months of minodronate treatment on the SOS and on the levels of bone turnover markers in Japanese postmenopausal women with an increased risk of fractures.

2. Methods

2.1. Ethics approval

The present study was performed at Hiyoshi Medical Clinic (Kanagawa, Japan). The protocol was approved by the Ethics Committee of Hiyoshi Medical Clinic (Kanagawa, Japan).

2.2. Study participants

Forty-two Japanese postmenopausal women with an increased risk of fractures who had been treated with a 50-mg monthly dose of minodronate for > 12 months were recruited at the outpatient clinic of Hiyoshi Medical Clinic (Kanagawa, Japan) during a 5-month period between January 7, 2014 and June 3, 2014. The dose of minodronate used in this study is the dose used in Japan to treat osteoporosis in postmenopausal women, and its safety and efficacy have been demonstrated.[2] Patients were eligible if they had postmenopausal osteoporosis or osteopenia with a clinical risk factor for fractures. The clinical risk factors for fractures included current smoking, a maternal history of hip fractures, and daily alcohol consumption of $\geq$ 2 units.[8] According to the Japanese diagnostic criteria,[9,10] osteoporosis is defined as (1) BMD < 70% of the young adult mean (YAM) or the "presence" of osteopenia on X-ray images of the spine and (2) BMD of 70−80% of the YAM or "possible" osteopenia on X-ray images of the spine and a history of osteoporotic fractures. Dual-energy X-ray absorptiometry of the spine is useful for monitoring osteoporosis in Japanese women and QUS is apparently less useful,[11] therefore osteoporosis the was diagnosed by using the SOS (i.e., < 70% of the YAM or 70−80% of the YAM and a history of osteoporotic fractures) and the X-ray findings of the spine (i.e., "presence" of osteopenia or "possible" osteopenia along with a history of osteoporotic fractures). Osteopenia was defined as a BMD between 70% and 80% of the YAM but without any history of osteoporotic fractures.[9,10] Patients were excluded if they had a history of reflux esophagitis, gastric or duodenal ulcer, gastrectomy, renal failure, or bone diseases such as cancer-induced bone loss because of aromatase inhibitors, primary hyperparathyroidism, hyperthyroidism, Cushing's syndrome, multiple myeloma, Paget's disease of the bone, rheumatoid arthritis, or osteogenesis imperfecta.

The assessment before the start of minodronate treatment included a medical history, physical examination, plain radiography of the thoracic and lumbar spine, measurement of the SOS of the calcaneus, and biochemical tests of the blood (e.g., serum calcium, phosphorus, and ALP) and urine (e.g., NTX). The urinary NTX levels were also 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. We evaluated the outcome of minodronate treatment after 12 months. The compliance of all patients for 12-month minodronate treatment was > 90%.

2.3. Assessment of morphometric vertebral fractures

Plain lateral X-ray films of the thoracic and lumbar spine were obtained at the start of treatment to detect evidence of morphometric vertebral fractures. According to the Japanese criteria, a vertebral fracture is defined in accordance with the vertebral height on lateral X-ray films.[9,10] In brief, the vertebral height is measured at the anterior (A), central (C), and posterior (P) parts of the vertebral body. A vertebral fracture is defined as (1) a $\geq$ 20% reduction in the vertebral height (A, C, and P), compared to the height of the adjacent vertebrae; (2) a C/A or C/P ratio of < 0.8; or (3) an A/P ratio of < 0.75. Vertebral fractures were assessed at the T4−L4 level.

2.4. Assessment of clinical vertebral and nonvertebral fractures

Low-traumatic osteoporotic clinical fractures were assessed. Clinical vertebral fractures were determined by the clinical symptoms and findings on radiographic or magnetic resonance images of the lumbar and thoracic spine. Nonvertebral fractures such as major osteoporotic fractures of the distal radius, proximal humerus, and hip were determined by clinical symptoms and radiographic images of the wrist, shoulder, and hip joints, respectively.

2.5. Measurement of levels of serum calcium, phosphorus, and ALP and urinary NTX

The serum calcium, phosphorus, and ALP levels were measured using standard laboratory techniques. The urinary NTX levels were measured using an enzyme immunoassay (EIA).

2.6. Measurement of SOS of the calcaneus

The SOS of the left calcaneus was measured using a QUS device (CM-200; Elk Corp., Osaka, Japan). The reliability and reproducibility of this QUS device has already been reported, and the coefficient of variation is 0.15% using the phantom technique and 0.27% *in vivo*.[12]

2.7. Statistical analysis

Data were expressed as the mean ± standard deviation (SD). The one-way analysis of variance (ANOVA) with repeated measurements test was used to determine the significance of the longitudinal changes in the SOS and biochemical markers. The ANOVA with Fisher's protected least significant difference (PLSD) test was used to perform multiple comparisons of the SOS and biochemical markers among the time points. All statistical analyses were performed using StatView-J5.0 software (SAS Institute, Cary, NC, USA) on a Windows computer. A significance level of $p < 0.05$ was used for all the comparisons.

3. Results

3.1. Characteristics of the study participants at the start of treatment

Table 1 shows the anthropometry, SOS, and biochemical markers of the study participants at the start of treatment. The mean age of the women was 71.8 years (range, 55–84 years). The mean SOS was 1475 m/s, which corresponds to 68.2% of the YAM. The mean serum calcium, phosphorus, and ALP levels were 9.2 mg/dL, 3.3 mg/dL, and 233 IU/L, respectively, which were within the normal ranges (8.4–10.2 mg/dL, 2.5–4.5 mg/dL, and 100–340 IU/L, respectively). The mean urinary NTX level was 53.5 nmol bone collagen equivalent (BCE)/mmol creatinine (Cr), which was relatively high but still within the normal range for Japanese women (9.3–54.3 nmol BCE/mmol Cr).[13]

3.2. Changes in the SOS of the calcaneus

Fig. 1 shows the changes in the SOS of the calcaneus. One-way ANOVA with repeated measurements test showed a significant longitudinal increase in the SOS at 12 months ($p = 0.0012$). ANOVA with Fisher's PLSD test showed a significant increase in the SOS at 12 months ($p < 0.05$). The mean percent change in the SOS from the baseline after 12 months of treatment was +0.47% (Table 2), which were higher than the coefficient of variation *in vivo* (0.27%).[12]

Table 1
Baseline anthropometry, SOS, and biochemical markers of the study participants.

	Mean ± SD	Range[a]
Age (y)	71.8 ± 7.3	55–84
Height (m)	1.54 ± 0.05	1.43–1.67
Body weight (kg)	50.9 ± 6.6	36–63
Body mass index (kg/m^2)	21.5 ± 2.4	15.6–27.9
SOS (m/s)	1475 ± 15	1441–1498
SOS as % of YAM	68.2 ± 6.8	53–79
Calcium (mg/dL)	9.2 ± 0.3	8.4–10.0
Phosphorus (mg/dL)	3.3 ± 0.5	1.6–4.6
ALP (IU/L)	233 ± 70	116–416
Urinary NTX (nM BCE/mM Cr)	53.5 ± 15.8	24.6–86.7

ALP = alkaline phosphatase; BCE = bone collagen equivalent; Cr = creatinine; NTX = cross-linked N-terminal telopeptides of type I collagen; SD = standard deviation; SOS = speed of sound; YAM = young adult mean.

[a] The normal ranges of serum calcium, phosphorus, and ALP are 8.4–10.2 mg/dL, 2.5–4.5 mg/dL, and 100–340 IU/L, respectively. The standard range of urinary NTX is 9.3–54.3 nM BCE/mM Cr. The cutoff values for bone loss and vertebral fracture risk are 35.3 nM BCE/mM Cr and 54.3 nM BCE/mM Cr, respectively.

3.3. Changes in biochemical markers

Fig. 2 shows the changes in the biochemical markers. After 3 months of treatment, the mean urinary NTX levels had decreased (26.0 ± 8.6 nmol BCE/mmol Cr). The mean serum ALP levels also decreased during the 12-month treatment

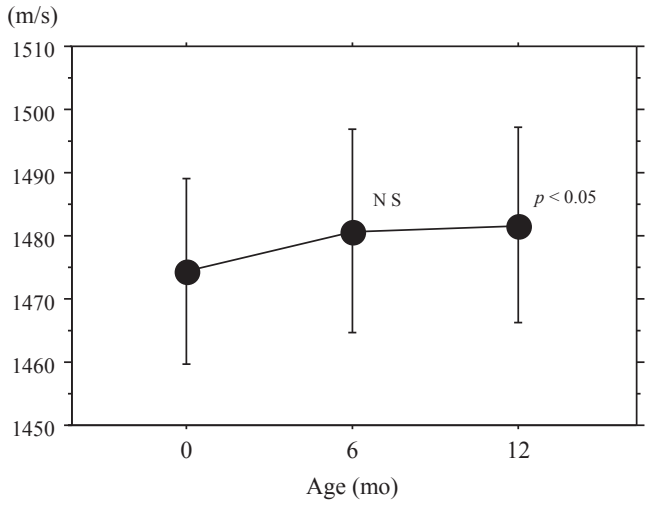

Fig. 1. Change in the speed of sound. Data are expressed as mean ± standard deviation. A one-way analysis of variance (ANOVA) with repeated measurements was used to determine the significance of the longitudinal changes in the SOS. ANOVA with Fisher's protected least significant difference (PLSD) test was used to perform multiple comparisons of the speed of sound among time points. One-way ANOVA with repeated measurements showed a significant longitudinal increase in the SOS at 12 months ($p = 0.0012$). ANOVA with Fisher's PLSD test showed a significant increase in the SOS at 12 months ($p < 0.05$). NS = not significant; SOS = speed of sound.

Table 2
Percent changes in SOS and biochemical markers.

	3 mo	6 mo	12 mo
SOS		0.40 ± 0.62	0.47 ± 0.95
Calcium		−0.5 ± 4.1	−0.8 ± 4.0
Phosphorus		3.0 ± 16.9	−1.8 ± 19.2
ALP		−21.9 ± 14.7	−25.8 ± 14.0
Urinary NTX	−47.5 ± 21.1		

Data are presented as mean ± SD.
ALP = alkaline phosphatase; NTX = cross-linked N-terminal telopeptides of type I collagen; SD = standard deviation; SOS = speed of sound.

period (167 ± 44 IU/L). One-way ANOVA with repeated measurements showed significant longitudinal decreases in the serum ALP and urinary NTX levels (for both, $p < 0.0001$). ANOVA with Fisher's PLSD test showed significant decreases in the serum ALP and urinary NTX levels (for both, $p < 0.0001$). There were no significant changes in the serum calcium or phosphorus levels. After 3 months of treatment, the mean percent change in the urinary NTX level from the baseline was a decrease of 47.5% (Table 2), whereas the change for the serum ALP levels after 6 months and 12 months of treatment was a decrease of 21.9% and 25.8%, respectively (Table 2).

3.4. Clinical fractures

During the 12-month treatment period, only one patient experienced a rib fracture.

3.5. Adverse events

No serious adverse events, such as osteonecrosis of the jaw, femoral diaphysis atypical fractures, or atrial fibrillation occurred in the present study, although such events have been reported in other studies.[14–16]

4. Discussion

The present study confirmed that treatment with minodronate decreased the urinary NTX by 47.5% at 3 months and serum ALP levels by 25.8% at 12 months and elicited a modest increase of 0.47% in the SOS of the calcaneus at 12

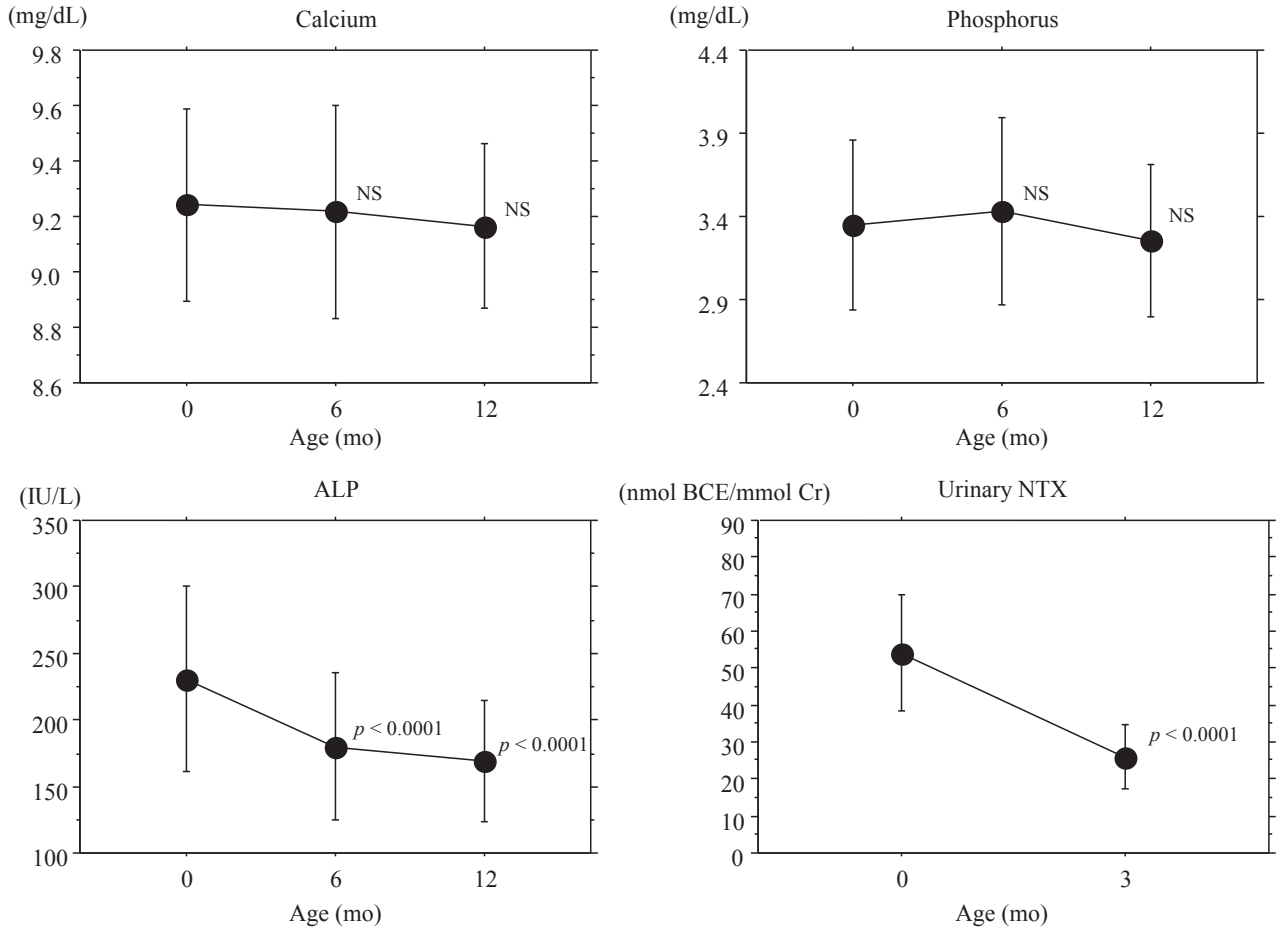

Fig. 2. Changes in biochemical markers. Data are expressed as mean ± standard deviation. One-way analysis of variance (ANOVA) with repeated measurements was used to determine the significance of the longitudinal changes in the biochemical markers. ANOVA with Fisher's protected least significant difference (PLSD) test was used to perform multiple comparisons of the biochemical markers among time points. One-way ANOVA with repeated measurements showed significant longitudinal decreases in serum ALP and urinary NTX levels (both $p < 0.0001$). ANOVA with Fisher's PLSD test showed significant decreases in serum ALP and urinary NTX levels (both $p < 0.0001$). There were no significant changes in serum calcium or phosphorus levels. ALP = alkaline phosphatase; Cr = creatinine; BCE = bone collagen equivalent; NS = not significant; NTX = cross-linked N-terminal telopeptides of type I collagen.

months in Japanese postmenopausal women with an increased risk of fractures. The objectives of this study were to determine (1) whether decreases in bone turnover markers would be similar to those reported in previous studies and (2) whether the increase in the SOS of the calcaneus would be significantly greater than the range of reproducibility. We also compared the effects of minodronate and those of alendronate and risedronate on the changes in these parameters.

The urinary NTX levels were measured at 3 months after the start of treatment because the measurement of urinary NTX levels at this time helps assess whether the antiresorptive effects of minodronate are sufficient or clinically significant.[2] A previous RCT showed that a 50-mg monthly dose of minodronate with calcium and vitamin D supplementation decreases urinary NTX by ~55% at 3 months and decreases serum bone-specific ALP by ~55% at 12 months in Japanese patients with involutional osteoporosis.[2] However, no data have been presented with regard to serum ALP. The 47.5% decrease in the urinary NTX levels in the present study was smaller than the decrease in a previous RCT.[2] One reason for this discrepancy is that calcium and vitamin D supplementation were not used in the present study, unlike the protocol in a previous RCT.[2] This current clinical practice-based observational study nevertheless confirmed that treatment with minodronate for 12 months suppressed bone turnover in postmenopausal women with an increased risk of fractures. In the beginning of medication, by using brochures, we instructed the patients to consume 800 mg of calcium and 800 IU of vitamin D every day. Optimal vitamin D repletion is believed to be necessary to maximize the response to antiresorbers in BMD changes and to reduce the risk of fracture in postmenopausal women with osteoporosis.[17] Thus, improvements in the vitamin D status may be necessary for greater responses of the SOS and bone turnover markers to minodronate.

The mean age of the study participants at the start of treatment was 71.8 years. The reference values of the SOS of the calcaneus in healthy Japanese women aged 65−69 years, 70−74 years, and 75−79 years are 1487 m/s, 1481 m/s, and 1475 m/s, respectively.[18] Treatment with minodronate increased the SOS of the calcaneus from 1475 m/s at the start of treatment to 1481 m/s at 12 months. Therefore, it seems that minodronate may help to increase the SOS of the calcaneus in postmenopausal women with an increased risk of fractures. At 12 months, the percent increase in SOS from the baseline was 0.47%. This increase appeared to be modest, although it likely exceeded the coefficient of variation (CV) of the SOS of the calcaneus *in vivo* (0.27%).[12]

The present study was a single-arm study. However, our previous studies may act as a reference to show the potential benefits of minodronate over alendronate or risedronate. We previously reported the effects of 12 months of treatment with alendronate (35 mg weekly) and risedronate (17.5 mg weekly) on the SOS and on bone turnover markers in postmenopausal women with osteoporosis (mean age, 69.0 years and 71.1 years, respectively).[6,7] At 3 months after the start of treatment, alendronate and risedronate reduced the urinary levels of NTX by 44.9% and by 34.7%, respectively; at 12 months, alendronate and risedronate reduced the serum levels of ALP by 22.2% and 21.2%, respectively, and increased the SOS of the calcaneus by 0.6% and 0.65%, respectively. In the present study, minodronate (50 mg monthly) decreased the urinary NTX levels by 47.5% at 3 months and the serum levels of ALP by 25.8% at 12 months, and increased the SOS of the calcaneus by 0.47% at 12 months in postmenopausal women with an increased risk of fractures (mean age, 71.8 years). Thus, the reductions in the urinary levels of NTX were greater with minodronate than with alendronate or risedronate. This finding is consistent with the results of RCTs.[19,20] However, the increase in the SOS was not greater with minodronate than with alendronate or risedronate, which suggests that the reduction in bone turnover may not reflect the improvement of bone structure and quality.

The present study had notable limitations. First, the study had a retrospective design and a relatively small sample size, and the data were collected by conventional medical practices. Second, the study had no control group. Third, there are no data regarding the long-term reproducibility of QUS parameter measurements. Fourth, the participants did not receive either elemental calcium or natural vitamin D supplementation. Natural vitamin D supplementation is not prevalent in Japan. This circumstance makes it difficult to compare the present study with other studies because most other studies have involved patients with osteoporosis who have received calcium and vitamin D supplements. Thus, prospective studies with a large number of participants are needed to verify the efficacy and safety of minodronate in combination with calcium and vitamin D supplementation in Japanese postmenopausal women with an increased risk of fractures.

In conclusion, the present study confirmed that minodronate suppresses bone turnover, and produces a modest but significant increase in the SOS of the calcaneus in Japanese postmenopausal women with an increased risk of fractures. The results of this study and our previous studies suggest that alendronate, risedronate, and minodronate have beneficial effects on bone turnover markers and on the SOS of the calcaneus.

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