turnover in osteoporosis (2004). J Bone Miner Metab. 2005;23:97–104.
15. Somford MP, Draijer FW, Thomassen BJW, Chavassieux PM, Boivin G, Papapoulos SE. Bilateral fractures of the femur diaphysis in a patient with rheumatoid arthritis on long-term treatment with alendronate: clues to mechanism of increased bone fragility. J Bone Miner Res. 2009;24:1736–40.
16. Abrahamsen B, Eiken P. Eastell R Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. J Bone Miner Res. 2009;24:1095–102.

J Bone Miner Metab
DOI 10.1007/s00774-010-0242-8

ORIGINAL ARTICLE

Hip structure analysis of bisphosphonate-treated Japanese postmenopausal women with osteoporosis

Junichi Takada · Genichiro Katahira · Kousuke Iba · Takashi Yoshizaki · Toshihiko Yamashita

Received: 7 June 2010 / Accepted: 7 October 2010

Abstract The purpose of this study was to clarify the effects of a 1-year treatment with either alendronate or risedronate on the proximal femoral geometry among Japanese women with osteoporosis by hip structure analysis. Postmenopausal women who had taken at least 90% of their prescription for alendronate (35 mg/week, 94 patients) or risedronate (17.5 mg/week, 181 patients) for 1 year were retrospectively analyzed. In the alendronate treatment group, bone mineral density (BMD), cross-sectional area (CSA), section modulus and average cortex significantly increased by 0.81, 1.35, 2.23 and 0.97% at the narrow neck and increased by 2.19, 2.28, 2.85 and 1.11% at the intertrochanteric, respectively. Buckling ratio at the intertrochanteric significantly decreased by 2.50%. The CSA, section modulus and average cortex at the shaft significantly increased at 1 year. In the risedronate treatment group, the CSA, section modulus and average cortex at the narrow neck significantly increased by 0.80, 0.95 and 0.89%, respectively. BMD, CSA, section modulus, and average cortex at the intertrochanteric significantly increased by 1.61, 0.88, 2.05 and 0.79%, respectively, and buckling ratio significantly decreased by 1.53%. BMD, CSA, section modulus, and average cortex at the shaft significantly increased. The percent change of section modulus was significantly correlated with that of BMD, CSA and average cortex and negatively correlated with that of buckling ratio at all regions in both treatment groups. Statistically significant differences between the alendronate and risedronate groups were seen for section modulus in the narrow neck and CSA in the intertrochanteric. In conclusion, Japanese osteoporotic women treated by either alendronate or risedronate showed significant improvements of geometry in proximal femur within 1 year.

Keywords Hip structure analysis · Geometry · Alendronate · Risedronate · Bisphosphonate

J. Takada · K. Iba · T. Yamashita
Department of Orthopedic Surgery, Sapporo Medical University, Sapporo, Japan

J. Takada (✉) · T. Yoshizaki
Kitago Orthopedic Clinic, Kitago, 3jyo-8, 5-33, Shiroishi-ku, Sapporo 003-0833, Japan
e-mail: jtakada@kitago-ortho.com

G. Katahira
Sapporo Kiyota Orthopaedic Hospital, Sapporo, Japan

Introduction

Areal bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DXA) is a valuable tool for the evaluation of bone fragility, and shows significant correlation between BMD decline and risk of fracture [1–3]. However, BMD may not be the best assessment of treatment efficacy since the fracture reduction after treatment is only partially explained by increased BMD [4–6]. Strength of bone is governed by structural dimensions and tissue material properties, neither of which is directly measured by a conventional BMD measurement.

Beck and Ruff applied the hip structure analysis (HSA) method to measure proximal femur geometry and strength using conventional DXA scans of the hip [7, 8]. HSA has been used to demonstrate age trends, racial and gender differences, and treatment effects on osteoporosis in Caucasians [8–16]. In Japan, we have previously demonstrated age-related differences in structural geometry and femoral

Published online: 30 November 2010

strength [17] and raloxifene had positive effects on geometry in Japanese women with osteoporosis [18]. Ito et al. [19] also reported that minodronic acid hydrate, a new bisphosphonate developed in Japan, improved bone strength indices in the proximal femoral region.

Bonnick et al. [15] reported that treatment with once-weekly alendronate or risedronate resulted in significant improvements in HSA parameters in Caucasian patients with osteoporosis; however, the doses of bisphosphonates for Japanese patients are half of those applied to Caucasians (alendronate 70 vs. 35 mg/week, risedronate 35 vs. 17.5 mg/week, in Caucasians vs. Japanese, respectively). These dosages seemed to be associated with race differences [20, 21]. The HSA for minodronic acid in Japanese women has been previously reported [19]; however, the effects of bisphosphonates are not the same. These results indicate that analysis of the geometry for the half doses of alendronate and risedronate is necessary in Japanese patients with osteoporosis.

The purpose of this study was to clarify the effects of a 1-year treatment with either alendronate (35 mg/week) or risedronate (17.5 mg/week) on the proximal femoral geometry of Japanese postmenopausal women with osteoporosis by HSA.

Materials and methods

Three hundred and sixty-seven community-dwelling, ambulatory, postmenopausal women had taken alendronate (35 mg/week, 128 patients) or risedronate (17.5 mg/week, 239 patients) from August 2007 to April 2009. Of these patients, 275 of them who had taken at least 90% of their prescribed biphosphonates for 1 year were retrospectively analyzed by HSA. The number of patients and the mean age was 94 patients and 73.2 years of age for alendronate and 181 patients and 70.6 years of age for risedronate, respectively. There was no significant difference between alendronate and risedronate in the percent of patients who dropped out and/or discontinued medication (26.6% in alendronate, 24.3% in risedronate). All of the patients in both treated groups were defined by Japanese osteoporosis diagnosis criteria [22]. These criteria included low BMD (T score <-2.5) or presence of osteoporotic fractures. Patients with a history of hip fracture or any disease or medication known to affect bone metabolism were excluded from the study. DXA scans of the hip were taken at baseline and were repeated at 6 and 12 month follow-up. Hip scans were performed using a hip positioner system (HPS; OsteoDyne, Durham, NC, USA) to ensure consistent positioning [23]. This device keeps the subject's legs positioned in abduction and internal rotation (15°).

Hip structure analysis (HSA)

The archived DXA images were analyzed using the HSA method which is described in detail in earlier publications [7, 8]. Briefly, using an automated program, DXA scan files were first converted into bone mass images in which pixel values represent bone mass in grams per square centimeter. The underlying principle of the method is that a line of pixels traversing the bone axis is a projection of the corresponding cross-section from which certain geometric properties can be derived. Three measured sites were defined as: (1) narrow neck, traversing the narrowest width of the femoral neck, (2) intertrochanteric, along the bisector of the shaft and femoral neck axes, and (3) shaft, at a distance of 1.5 times minimum neck width, distal to the intersection of the neck and shaft axes. HSA was performed by a radiological engineer who did not know about the treatment of the patients.

The structural parameters used in this paper were as follows [24, 25].

- Areal BMD (g/cm^2): mean values of BMD from the narrow neck region are on the average about 14% higher than the conventional Hologic neck region of interest (ROI) values on the same subjects, although age trends are similar in previous reports [10].
- Outer diameter (cm): the distance between (blur corrected) outer margins of the cross-section.
- Cross-sectional area (CSA, cm^2): this is defined as the surface area of bone tissue in the cross-section after excluding soft tissue (marrow) spaces. CSA is an index of resistance to forces directed along the long axis of the bone.
- Section modulus (cm^3): this is an index of resistance to bending forces and is calculated as CSMI/d_{max} where CSMI is the cross-sectional moment of inertia and d_{max} is the maximum distance from either bone edge to the centroid of the profile.
- Average cortex (cm): this is an estimate of the mean cortical thickness assuming a circular (narrow-neck or shaft) or elliptical (intertrochanteric) annulus model of the cross-section for use in the estimated buckling ratio. The model assumes that 60, 70 and 100% of the measured bone mass is in the cortex for narrow-neck, intertrochanteric and shaft, respectively.
- Buckling ratio: this describes stable configurations of thin-walled tubes subjected to compressive loads and is estimated as the ratio of d_{max} to the estimated mean cortical thickness. Buckling ratio is presented only for the narrow neck and intertrochanteric regions, because this parameter is not important in the shaft.

Based on a preceding study, precision error (%CV) for HSA parameters at the neck, intertrochanteric and shaft ranges from 0.8 to 4.7%, with an average of 2.2% [17, 26].

Statistical analysis

All parameters are presented as mean (standard deviations, SD) at baseline, and percent differences from baseline (95% confidence interval, CI). Differences were regarded as statistically significant when the 95% CI did not include zero. The correlations between HSA parameters were analyzed by Pearson's R and considered statistically significant at $P < 0.05$. P values from two-sample t tests were used to compare group means and considered statistically significant at $P < 0.05$.

Results

Percent changes from baseline in HSA parameters

Alendronate treatment group

Narrow neck: BMD significantly increased by 0.81% (95% CI 0.16, 1.45) at 1 year, and section modulus significantly increased by 0.86% (95% CI 0.16, 1.56) and 2.23% (95% CI 1.47, 2.99) compared to baseline at 6 months and 1 year, respectively. Compared to baseline, the mean difference in CSA and average cortex significantly increased at 1 year; however, changes in the outer diameter and buckling ratio did not reach significance (Table 1a).

Intertrochanteric: BMD and section modulus significantly increased by 1.20% (95% CI 0.58, 1.81) and 1.24% (95% CI 0.62, 1.85) at 6 months, by 2.19% (95% CI 1.38, 3.01) and 2.85% (95% CI 1.98, 3.72) at 1 year, respectively. The buckling ratio significantly decreased by 1.30% (95% CI −2.12, −0.49) and 2.50% (95% CI −3.40, −1.59) at 6 months and 1 year, respectively. The other parameters, CSA and average cortex significantly increased at 1 year; however, changes in the outer diameter did not show significant change (Table 1b).

Shaft: CSA, section modulus and average cortex significantly increased at 1 year; however, changes in BMD and the outer diameter did not show significant change (Table 1c).

Percent changes from baseline in HSA parameters

Risedronate treatment group

Narrow neck: the section modulus significantly increased by 0.95% (95% CI 0.19, 1.70) compared to baseline at 1 year. Compared to baseline, CSA and average cortex significantly increased at 1 year; however, changes in

Table 1 Mean (SD) bone values at baseline and mean percent difference (95% CI) from baseline in alendronate

	Baseline values	% Difference from baseline mean (95% CI)	
	Mean (SD)	6 months	12 months
a: Narrow neck			
BMD (g/cm^2)	0.801 (0.153)	0.37 (−0.15, 0.88)	0.81 (0.16, 1.45)*
CSA (cm^2)	2.320 (0.448)	0.56 (0.02, 1.09)*	1.35 (0.71, 2.00)*
Outer diameter (cm)	3.047 (0.189)	0.13 (−0.16, 0.42)	0.28 (−0.09, 0.66)
Section modulus (cm^3)	1.071 (0.223)	0.86 (0.16, 1.56)*	2.23 (1.47, 2.99)*
Average cortex (cm)	0.154 (0.031)	0.47 (−0.03, 0.97)	0.97 (0.13, 1.81)*
Buckling ratio	11.323 (2.481)	0.14 (−0.82, 1.10)	−0.79 (−1.77, 0.20)
b: Intertrochanteric			
BMD (g/cm^2)	0.799 (0.161)	1.20 (0.58, 1.81)*	2.19 (1.38, 3.01)*
CSA (cm^2)	4.025 (0.867)	0.82 (0.26, 1.38)*	2.28 (1.65, 2.92)*
Outer diameter (cm)	5.292 (0.333)	0.08 (−0.30, 0.45)	0.13 (−0.40, 0.66)
Section modulus (cm^3)	3.496 (0.796)	1.24 (0.62, 1.85)*	2.85 (1.98, 3.72)*
Average cortex (cm)	0.336 (0.077)	0.33 (−0.19, 0.85)	1.11 (0.45, 1.77)*
Buckling ratio	9.377 (2.168)	−1.30 (−2.12, −0.49)*	−2.50 (−3.40, −1.59)*
c: Shaft			
BMD (g/cm^2)	1.413 (0.266)	0.21 (−0.39, 0.82)	0.62 (−0.18, 1.42)
CSA (cm^2)	3.837 (0.705)	0.43 (−0.22, 1.08)	1.18 (0.44, 1.92)*
Outer diameter (cm)	2.860 (0.183)	0.22 (−0.11, 0.54)	0.23 (−0.17, 0.63)
Section modulus (cm^3)	2.093 (0.384)	0.49 (−0.18, 1.15)	1.08 (0.31, 1.85)*
Average cortex (cm)	0.539 (0.147)	0.43 (−0.33, 1.18)	1.03 (0.07, 2.00)*

BMD bone mineral density, *CSA* cross-sectional area, *SD* standard deviations, *CI* confidence interval

* $P < 0.05$ versus baseline

Table 2 Mean (SD) bone values at baseline and mean percent difference (95% CI) from baseline in risedronate

	Baseline values	% Difference from baseline mean (95% CI)	
	Mean (SD)	6 months	12 months
a: Narrow neck			
BMD (g/cm^2)	0.760 (0.136)	−0.06 (−0.60, 0.48)	0.35 (−0.39, 1.08)
CSA (cm^2)	2.200 (0.393)	0.33 (−0.26, 0.91)	0.80 (0.09, 1.50)*
Outer diameter (cm)	3.048 (0.215)	0.19 (−0.18, 0.56)	0.25 (−0.07, 0.57)
Section modulus (cm^3)	1.017 (0.221)	0.39 (−0.16, 0.94)	0.95 (0.19, 1.70)*
Average cortex (cm)	0.146 (0.028)	0.33 (−0.21, 0.86)	0.89 (0.13, 1.66)*
Buckling ratio	12.143 (3.117)	−0.35 (−1.11, 0.41)	−0.81 (−1.86, 0.24)
b: Intertrochanteric			
BMD (g/cm^2)	0.753 (0.170)	0.90 (0.48, 1.31)*	1.61 (1.05, 2.17)*
CSA (cm^2)	3.733 (0.829)	0.47 (0.07, 0.87)*	0.88 (0.33, 1.43)*
Outer diameter (cm)	5.239 (0.404)	0.13 (−0.12, 0.38)	0.21 (−0.14, 0.56)
Section modulus (cm^3)	3.180 (0.858)	1.00 (0.52, 1.49)*	2.05 (1.29, 2.80)*
Average cortex (cm)	0.315 (0.073)	0.28 (−0.12, 0.68)	0.79 (0.22, 1.37)*
Buckling ratio	10.105 (2.968)	−0.57 (−1.10, −0.04)*	−1.53 (−2.25, −0.81)*
c: Shaft			
BMD (g/cm^2)	1.344 (0.228)	0.24 (−0.33, 0.82)	0.75 (0.08, 1.43)*
CSA (cm^2)	3.612 (0.661)	0.34 (−0.21, 0.88)	0.98 (0.34, 1.62)*
Outer diameter (cm)	2.826 (0.219)	0.17 (−0.09, 0.44)	0.21 (−0.07, 0.49)
Section modulus (cm^3)	1.948 (0.417)	0.41 (−0.12, 0.95)	1.05 (0.38, 1.71)*
Average cortex (cm)	0.502 (0.110)	0.41 (−0.17, 0.98)	0.95 (0.20, 1.71)*

BMD bone mineral density, *CSA* cross-sectional area, *SD* standard deviations, *CI* confidence interval

* $P < 0.05$ versus baseline

BMD, the outer diameter and buckling ratio did not reach significance (Table 2a).

Intertrochanteric: BMD and section modulus significantly increased by 0.90% (95% CI 0.48, 1.31) and 1.00% (95% CI 0.52, 1.49) at 6 months, by 1.61% (95% CI 1.05, 2.17) and 2.05% (95% CI 1.29, 2.80) at 1 year, respectively. The buckling ratio significantly decreased by 0.57% (95% CI −1.10, −0.04) and 1.53% (95% CI −2.25, −0.81) at 6 months and 1 year, respectively. The other parameters, CSA and average cortex significantly increased at 1 year; however, changes in the outer diameter did not show significant change (Table 2b).

Shaft: BMD, CSA, section modulus and average cortex significantly increased at 1 year; however, changes in the outer diameter did not show significant change (Table 2c).

Correlations among the percent changes of parameters

Tables 3 and 4 show correlations (Pearson's R) among the percent changes of HSA parameters in the narrow neck, intertrochanteric and shaft regions. The percent change of the section modulus is significantly correlated with the percent change of BMD, CSA, and average cortex and negatively correlated with the percent change of the buckling ratio in all regions in both treatment groups. As expected, the percent changes of BMD had a positive relationship with the percent change of CSA, but negative relationship with the percent change of the outer diameter in all regions.

Comparisons of percent changes of the parameters between the alendronate and risedronate treatment groups

The comparisons of percent changes of the parameters between the alendronate and risedronate treatment groups are shown in Fig. 1. Statistically significant differences between alendronate and risedronate were seen for section modulus in the narrow neck and CSA in the intertrochanteric. The other parameters did not show a significant difference; however, alendronate showed a greater improvement in several parameters compared with risedronate.

Discussion

One of the problems with the use of BMD as a monitor for osteoporosis treatment is that it does not completely capture the mechanical factors that lead to fragility [4–6]. Beck and Ruff applied the HSA method to measure proximal femur geometry and strength using conventional DXA scans of the hip [7, 8]. In this study, we are the first to report that Japanese women with either alendronate or

Table 3 Cross-correlations (Peason's *R*) among the percent changes of parameters in alendronate

	BMD	CSA	Outer diameter	Section modulus	Average cortex	Buckling ratio
a: Narrow neck						
BMD	1.000	0.857**	−0.350**	0.394**	0.750**	−0.547**
CSA		1.000	−0.136	0.431**	0.633**	−0.527**
Outer diameter			1.000	0.120	−0.329**	0.274*
Section modulus				1.000	0.460**	−0.625**
Average cortex					1.000	−0.660**
Buckling ratio						1.000
b: Intertrochanteric						
BMD	1.000	0.664**	−0.575**	0.644**	0.721**	−0.742**
CSA		1.000	−0.346**	0.616**	0.690**	−0.625**
Outer diameter			1.000	−0.267*	−0.385**	0.541**
Section modulus				1.000	0.530**	−0.564**
Average cortex					1.000	−0.729**
Buckling ratio						1.000
c: Shaft						
BMD	1.000	0.792**	−0.412**	0.756**	0.921**	−0.895**
CSA		1.000	−0.103	0.766**	0.796**	−0.650**
Outer diameter			1.000	−0.239*	−0.389**	0.552**
Section modulus				1.000	0.724**	−0.677**
Average cortex					1.000	−0.880**
Buckling ratio						1.000

BMD bone mineral density, *CSA* cross-sectional area

* $P < 0.05$, ** $P < 0.001$

Table 4 Cross-correlations (Peason's *R*) among the percent changes of parameters in risedronate

	BMD	CSA	Outer diameter	Section modulus	Average cortex	Buckling ratio
a: Narrow neck						
BMD	1.000	0.831**	−0.494**	0.731**	0.952**	−0.911**
CSA		1.000	−0.205*	0.739**	0.805**	−0.724**
Outer diameter			1.000	−0.143	−0.466**	0.576**
Section modulus				1.000	0.706**	−0.648**
Average cortex					1.000	−0.896**
Buckling ratio						1.000
b: Intertrochanteric						
BMD	1.000	0.719**	−0.601**	0.529**	0.753**	−0.756**
CSA		1.000	−0.163	0.706**	0.814**	−0.655**
Outer diameter			1.000	−0.044*	−0.278**	0.382**
Section modulus				1.000	0.634**	−0.580**
Average cortex					1.000	−0.792**
Buckling ratio						1.000
c: Shaft						
BMD	1.000	0.881**	−0.475**	0.737**	0.950**	−0.877**
CSA		1.000	−0.179*	0.851**	0.857**	−0.787**
Outer diameter			1.000	−0.050	−0.469**	0.613**
Section modulus				1.000	0.723**	−0.615**
Average cortex					1.000	−0.886**
Buckling ratio						1.000

BMD bone mineral density, *CSA* cross-sectional area

* $P < 0.05$, ** $P < 0.001$

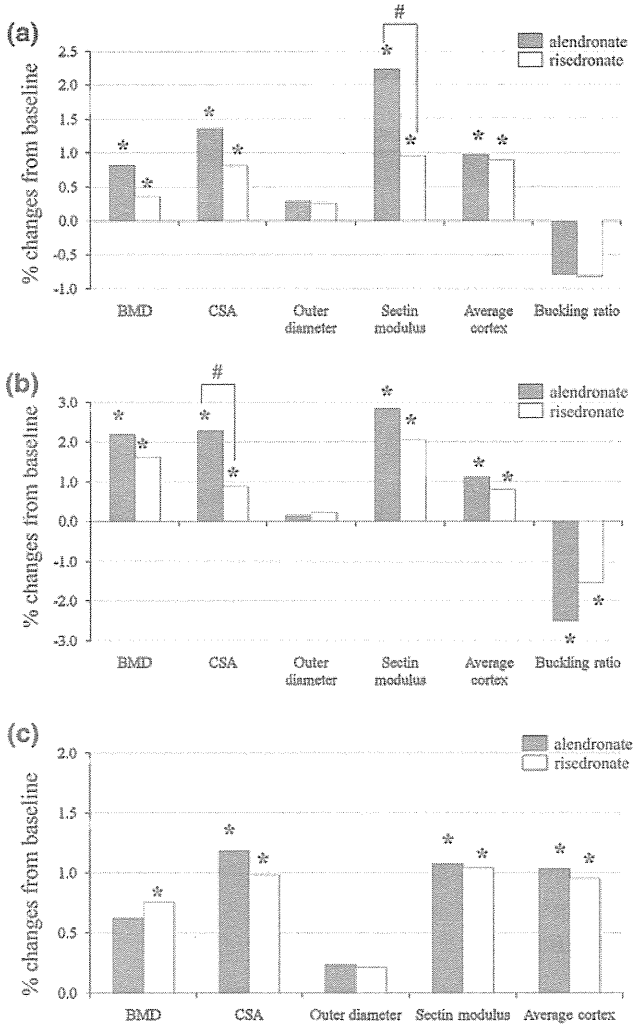


Fig. 1 Comparison of percent changes of the parameters between alendronate and risedronate at 1 year. **a** Narrow neck, **b** intertrochanteric, **c** shaft. *BMD* bone mineral density, *CSA* cross-sectional area. $^{\#}P < 0.05$ versus risedronate, $^{*}P < 0.05$ versus baseline

risedronate treatment over a 1-year period had significant improvements of geometry in proximal femur.

HSA has been demonstrated in the effects of alendronate and risedronate in the post hoc analysis of a large clinical trial (Fosamax Actonel Comparison Trial, FACT) in Caucasians [15]. Two years of treatment with either alendronate or risedronate resulted in statistically significant improvements from baseline in most geometric parameters at the narrow neck, intertrochanteric and shaft; however, these data are mainly based on Caucasian patients. It is not fully understood whether the geometric effects of bisphosphonate upon Japanese patients are the same on Caucasians, because the dosage used to treat osteoporosis in Japan (alendronate 35 mg/week, risedronate 17.5 mg/week) is half of that applied to Caucasians (alendronate 70 mg/week, risedronate 35 mg/week) [20, 21]. The HSA data for minodronic acid in Japanese women have been previously reported [19]; however, the effects of bisphosphonates are not the same. In addition, the changing trends of HSA parameters are not the same as those of BMD, so that the analysis of the half dosage of bisphosphonates to influence hip geometry is important.

It is worth noting that the percent change of section modulus was higher than that of BMD in all three regions (Tables 1, 2). These results might suggest that the reduction of fracture rate is not fully explained by increased BMD in the clinical outcomes. The baseline values of section modulus at all regions are greater than that of BMD, and the percent changes of section modulus are also greater than that of BMD; therefore, a small increase of absolute value in section modulus did not lead to a greater increase of percent changes.

The changing trends of HSA parameters in this study were generally consistent with the FACT study in mostly Caucasians, the minodronic acid study, and the raloxifene study in Japan (Table 5). These changes were particularly evident at the intertrochanteric region, i.e., BMD, CSA, section modulus, average cortex and buckling ratio showed significant improvements in the bisphosphonate and raloxifene treatments. CSA and section modulus at the narrow neck and average cortex at the shaft also showed a significant increase in all of the treatment groups. The tendency to change in the other parameters is approximately similar in the bisphosphonate and raloxifene treatment groups. In addition, the comparison of the percent changes of parameters between alendronate and risedronate showed that statistically significant differences were seen for section modulus in the narrow neck and CSA in the intertrochanteric. The other parameters did not show a significant difference; however, alendronate showed a greater improvement in several parameters compared with risedronate. Both alendronate and risedronate treatment over 1 year resulted in an improvement in HSA parameters with consistently greater effects seen with alendronate than risedronate. These consistent trends of efficacy in this study are approximately similar to the FACT study.

There are methodological limitations to our study. First, DXA scanners are not designed or optimized to measure structural dimensions. Precision in 3D was relatively poor in 2D. Second, use of 2D DXA scans means that the section modulus is assessed only in the scan plane; effects of treatment may be different for bending directions out of the image plane. Third, alendronate and risedronate significantly improved geometric parameters in Caucasians and Japanese; however, the magnitude of change in any of these parameters necessary to reduce hip fracture risk is unknown. Finally, the model assumes that 60, 70 and 100% of the measured bone mass is in the cortex for the narrow

Table 5 Comparison of changing trends of HSA parameters

	This study		Bonnick et al. [15]		Ito et al. [19]	Takada et al. [18]
	Alendronate (35 mg/week)	Risedronate (17.5 mg/week)	Alendronate (70 mg/week)	Risedronate (35 mg/week)	Minodronate (1 mg/day)	Raloxifene (60 mg/day)
Narrow neck						
BMD	↑	NS	↑	↑	↑	↑
CSA	↑	↑	↑	↑	↑	↑
Outer diameter	NS	NS	↑	↑	NS	↑
Section modulus	↑	↑	↑	↑	↑	↑
Average cortex	↑	↑	↑	↑	↑	NS
Buckling ratio	NS	NS	↓	NS	↓	NS
Intertrochanteric						
BMD	↑	↑	↑	↑	↑	↑
CSA	↑	↑	↑	↑	↑	↑
Outer diameter	NS	NS	NS	NS	NS	↑
Section modulus	↑	↑	↑	↑	↑	↑
Average cortex	↑	↑	↑	↑	↑	↑
Buckling ratio	↓	↓	↓	↓	↓	NS
Shaft						
BMD	NS	↑	↑	↑	↑	↑
CSA	↑	↑	↑	NS	↑	↑
Outer diameter	NS	NS	NS	↓	↑	↑
Section modulus	↑	↑	↑	NS	↑	↑
Average cortex	↑	↑	↑	↑	↑	↑

BMD bone mineral density, *CSA* cross-sectional area, *NS* not significant, ↑ significant increase from baseline, ↓ significant decrease from baseline

neck, intertrochanteric and shaft, respectively. These methods have the possibility of overestimating the cortical thickness in cases with increased trabecular bone, especially in the narrow neck and intertrochanteric regions.

Although there were some limitations, this study also has significant strengths. This is the first study employing the HSA method to examine whether geometric strength-related parameters in elderly Japanese women on either alendronate (35 mg/week) or risedronate (17.5 mg/week) alter femoral geometry in a positive direction within a 1 year period. Although these women maintained their hip BMD, there were statistically significant changes in the underlying geometry that has not previously been reported in Japanese women with osteoporosis. If geometric parameters better explain osteoporotic fragility than BMD, then alendronate and risedronate clearly change geometry toward improved strength at the femoral neck and intertrochanteric regions of Japanese women.

We conclude that Japanese women treated with either alendronate or risedronate for 1 year showed positive structural changes in proximal regions of the femur that suggest improved bending and axial strength.

Acknowledgments The authors wish to acknowledge Dr. Thomas J. Beck for his assistance.

References

1. Kanis JA (2002) Diagnosis of osteoporosis and assessment of fracture risk. Lancet 359:1929–1936
2. Miller PD (2003) Bone mass measurements. Clin Geriatr Med 19:281–297
3. Schott AM, Cormier C, Hans D, Favier F, Hausherr E, Dargent-Molina P, Delmas PD, Ribot C, Sebert JL, Breart G, Meunier PJ, for EPIDOS Group (1998) How hip and whole-body bone mineral density predict hip fracture in elderly women: the EPIDOS Prospective Study. Osteoporos Int 8:247–254
4. Li Z, Meredith MP, Hoseyni MS (2001) A method to assess the proportion of treatment effect explained by a surrogate endpoint. Stat Med 20:3175–3188
5. Cummings SR, Karpf DB, Harris F, Genant HK, Ensrud K, LaCroix AZ, Dennis M, Black DM (2002) Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. Am J Med 112:281–289
6. Sarkar S, Mitlak BH, Wong M, Stock JL, Black DM, Harper KD (2002) Relationships between bone mineral density and incident vertebral fracture risk with raloxifene therapy. J Bone Miner Res 17:1–10
7. Beck TJ, Ruff CB, Warden KE, Scott WW Jr, Rao GU (1990) Predicting femoral neck strength from bone mineral data: a structural approach. Invest Rad 25:6–18
8. Beck TJ, Ruff CB, Scott WW Jr, Plato CC, Tobin JD, Quan CA (1992) Sex differences in geometry of the femoral neck with aging: a structural analysis of bone mineral data. Calcif Tissue Int 50:24–29

9. Beck TJ, Ruff CB, Bissessur K (1993) Age-related changes in female femoral neck geometry: implications for bone strength. Calcif Tissue Int 53(Suppl 1):S41–S46
10. Beck TJ, Looker AC, Ruff CB (2000) Structural trends in the aging femoral neck and proximal shaft: analysis of the Third National Health and Nutrition Examination Survey dual-energy X-ray absorptiometry data. J Bone Miner Res 15:2297–2304
11. Wang XF, Duan Y, Beck TJ, Seeman E (2005) Varying contributions of growth and ageing to racial and sex differences in femoral neck structure and strength in old age. Bone 36:978–986
12. Uusi-Rasi K, Beck TJ, Semanick LM, Daphtary MM, Crans GG, Desaiah D, Harper KD (2006) Structural effects of raloxifene on the proximal femur: results from the multiple outcomes of raloxifene evaluation trial. Osteoporos Int 17:575–586
13. Greenspan SL, Beck TJ, Resnick NM, Bhattacharya R, Parker RA (2005) Effect of hormone replacement, alendronate, or combination therapy on hip structure geometry: a 3-year, double blind, placebo-controlled clinical trial. J Bone Miner Res 20:1525–1532
14. Uusi-Rasi K, Semanick LM, Zanchetta JR, Bogado CE, Eriksen EF, Sato M, Beck TJ (2005) Effects of teriparatide [rh PTH (1–34)] treatment on structural geometry of the proximal femur in elderly osteoporotic women. Bone 36:948–958
15. Bonnick SL, Beck TJ, Cosman F, Hochberg MC, Wang H, de Papp AE (2009) DXA-based hip structural analysis of once-weekly bisphosphonate-treated postmenopausal women with low bone mass. Osteoporos Int 20:911–921
16. Beck TJ, Lewiecki EM, Miller PD, Felsenberg D, Liu Y, Ding B, Libanati C (2008) Effects of denosumab on the geometry of the proximal femur in postmenopausal women in comparison with alendronate. J Clin Densitom 11:351–359
17. Takada J, Beck TJ, Iba K, Yamashita T (2007) Structural trends in the aging proximal femur in Japanese postmenopausal women. Bone 41:97–102
18. Takada J, Miki T, Imanishi Y, Nakatsuka K, Wada H, Naka H, Yoshizaki T, Iba K, Beck TJ, Yamashita T (2010) Effects of raloxifene treatment on structural geometry of the proximal femur in Japanese women with osteoporosis. J Bone Miner Metab 28:561–567
19. Ito M, Sone T, Fukunaga M (2010) Effect of minodronic acid hydrate on hip geometry in Japanese women with postmenopausal osteoporosis. J Bone Miner Metab 28:334–341
20. Uchida S, Taniguchi T, Shimizu T, Kakikawa T, Okuyama K, Okaniwa M, Arizono H, Nagata K, Santora AC, Shiraki M, Fukunaga M, Tomomitsu T, Ohashi Y, Nakamura T (2005) Therapeutic effects of alendronate 35 mg once weekly and 5 mg once daily in Japanese patients with osteoporosis: a double-blind, randomized study. J Bone Miner Metab 23:382–388
21. Kishimoto H, Fukunaga M, Kushida K, Shiraki M, Itabashi A, Nawata H, Nakamura T, Ohta H, Takaoka K, Ohashi Y, for the Risedronate Phase III Research Group (2006) Efficacy and tolerability of once-weekly administration of 17.5 mg risedronate in Japanese patients with involutional osteoporosis: a comparison with 2.5-mg once-daily dosage regimen. J Bone Miner Metab 24:405–413
22. Osteoporosis diagnostic criteria review committee: Japanese society for bone, mineral research (2001) Diagnostic criteria for primary osteoporosis: year 2000 revision. J Bone Miner Metab 19:331–337
23. Hans D, Duboeuf F, Schott AM, Horn S, Avioli LV, Drezner MK, Meunier PJ (1997) Effects of a new positioner on the precision of hip bone mineral density measurements. J Bone Miner Res 12:1289–1294
24. Ruff CB, Hayes WC (1983) Cross-sectional geometry of Pecos Pueblo femora and tibiae—a biomechanical investigation. I. Method and general patterns of variation. Am J Phys Anthropol 60:359–381
25. Melton LJ III, Beck TJ, Amin S, Khosla S, Achenbach SJ, Oberg AL, Riggs BL (2005) Contributions of bone density and structure to fracture risk assessment in men and women. Osteoporos Int 16:460–467
26. Nelson DA, Barondess DA, Hendrix SL, Beck TJ (2000) Cross-sectional geometry, bone strength, and bone mass in the proximal femur in black and white postmenopausal women. J Bone Miner Res 15:1992–1997

JOURNAL OF MEDICAL CASE REPORTS

CASE REPORT Open Access

Improvement of pain and regional osteoporotic changes in the foot and ankle by low-dose bisphosphonate therapy for complex regional pain syndrome type I: a case series

Yasuhisa Abe[1], Kousuke Iba[1*], Junichi Takada[2], Takuro Wada[1] and Toshihiko Yamashita[1]

Abstract

Introduction: Complex regional pain syndrome is characterized by pain, allodynia, hyperalgesia, edema, signs of vasomotor instability, movement disorders, joint stiffness, and regional osteopenia. It is recognized to be difficult to treat, despite various methods of treatment, including physiotherapy, calcitonin, corticosteroids, sympathetic blockade, and nonsteroidal anti-inflammatory drugs. Pathophysiologically, complex regional pain syndrome reveals enhanced regional bone resorption and high bone turnover, and so bisphosphonates, which have a potent inhibitory effect on bone resorption, were proposed for the treatment of complex regional pain syndrome.

Case presentation: A 48-year-old Japanese man with complex regional pain syndrome type I had severe right ankle pain with a visual analog scale score of 59 out of 100 regardless of treatment with physiotherapy and nonsteroidal anti-inflammatory drugs for five months. Radiographs showed marked regional osteoporotic changes and bone scintigraphy revealed a marked increase in radioactivity in his ankle. One month after the start of oral administration of risedronate (2.5 mg per day), his bone pain had fallen from a VAS score of 59 out of 100 to 18 out of 100. Bone scintigraphy at 12 months showed a marked reduction in radioactivity to a level comparable to that in his normal, left ankle. On the basis of these results, the treatment was discontinued at 15 months. At 32 months, our patient had almost no pain and radiographic findings revealed that the regional osteoporotic change had returned to normal.

A second 48-year-old Japanese man with complex regional pain syndrome type I had severe right foot pain with a visual analog scale score of 83 out of 100 regardless of treatment with physiotherapy and nonsteroidal anti-inflammatory drugs for nine months. Radiographs showed regional osteoporotic change in his phalanges, metatarsals, and tarsals, and bone scintigraphy revealed a marked increase in radioactivity in his foot. One month after the start of oral administration of alendronate (35 mg per week), his bone pain had fallen from a visual analog scale score of 83 out of 100 to 30 out of 100 and, at nine months, was further reduced to 3 out of 100. The treatment was discontinued at 15 months because of successful pain reduction. At 30 months, our patient had no pain and the radiographic findings revealed marked improvement in regional osteoporotic changes.

Conclusions: We believe low-dose oral administration of bisphosphonate is worth considering for the treatment of idiopathic complex regional pain syndrome type I accompanied by regional osteoporotic change.

* Correspondence: iba@sapmed.ac.jp
[1]Department of Orthopedic Surgery, Sapporo Medical University School of Medicine, Sapporo 060-8543, Japan
Full list of author information is available at the end of the article

Introduction

Complex regional pain syndrome (CRPS) is characterized by pain, allodynia, hyperalgesia, edema, signs of vasomotor instability, movement disorders, joint stiffness, and regional osteopenia [1,2]. Various methods of treatment - including physiotherapy, calcitonin, corticosteroids, sympathetic blockade, and nonsteroidal anti-inflammatory drugs (NSAIDs) - have been tried [3-5]. However, in many cases, pain and the ensuing loss of function are permanent despite treatment [2,6]. On the other hand, previous studies reported that accelerated and enhanced bone resorption and turnover play a central pathophysiological role in CRPS [6,7]. Accordingly, bisphosphonates, which have a potent inhibitory effect on bone resorption, were proposed for the treatment of CRPS. In fact, several studies indicated that the intravenous or high-dose oral administration of bisphosphonate improved pain and reduced bone turnover in CRPS cases [8-11]. In this report, we present two cases of CRPS in which a low dose of oral risedronate (2.5 mg per day) or alendronate (35 mg per week) markedly decreased pain and regional osteoporotic findings in the foot or ankle. Also, since the discontinuation of the bisphosphonate treatment, our patients have not complained of bone pain, and normal bone turnover has been observed for more than one year of follow-up without additional treatment.

Case presentation

A 48-year-old Japanese man with CRPS was referred to our institute for the treatment of severe right ankle pain with a visual analog scale (VAS) [12] score of 59 out of 100. About five months earlier, he began to feel severe right ankle pain without any trigger events. Although treatment, including physiotherapy and NSAID administration, was initiated in another clinic, the pain in his ankle progressively worsened and he demonstrated gait disturbance. A physical examination revealed redness, swelling, and remarkable tenderness around his ankle. Severe pain and hyperalgesia also resulted in the disturbance of ankle motion and weight-bearing. Radiographs showed marked regional osteoporotic changes in the distal tibia and fibula at his right ankle compared with his left ankle (Figure 1A). Bone scintigraphy with ^{99} ^{m}Tc-methylene diphosphonate revealed a marked increase in radioactivity in the bones around his ankle (Figure 1B). These clinical findings were consistent with CRPS type I (CRPS I) according to criteria of the International Association for the Study of Pain [2]. His lumbar bone mineral density was 0.904 g/cm^2, which is more than 80% of the Japanese young adult mean (YAM). Laboratory tests showed urinary crosslinked N-telopeptides of type I collagen (NTX), a bone resorption marker, to be 37.6 nmol bone collagen equivalent/mmol·Cr (nMBCE/mM·CR) (normal range, 9.3 to 54.3) and an alkaline phosphatase (ALP) level of 215 U/L (normal range, 110 to 370). Serum calcium (9.1 mg/dL; normal range 8.4 to 10.4), serum phosphate (2.9 mg/dL; normal range, 2.5 to 4.5), white blood cell count (5600/μL; normal range, 3900 to 9800), and C-reactive protein (< 0.1 mg/dL; normal range, < 0.3) were all at normal levels.

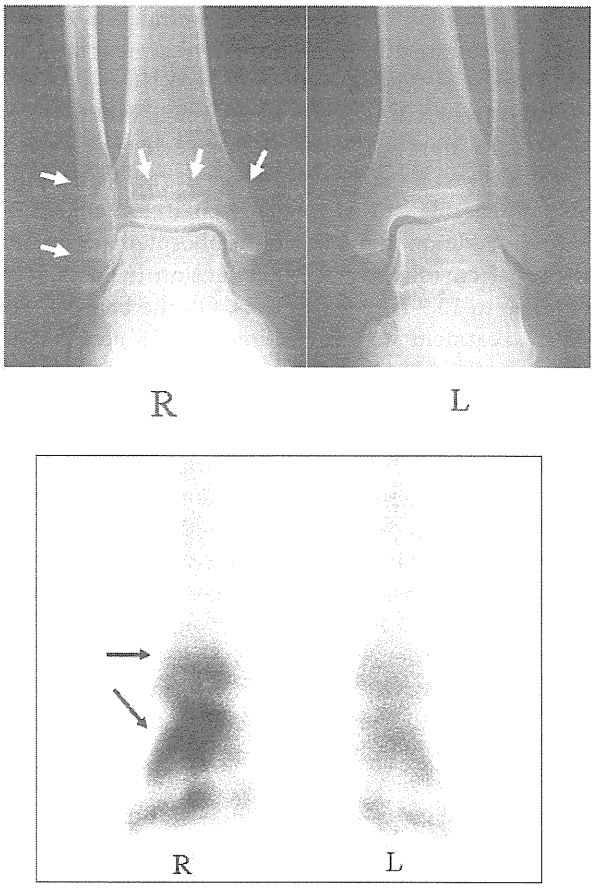


Figure 1 Radiographs (A) and scintigraphs (B) of the both ankles before treatment. The radiograph of the right ankle showed regional osteoporotic findings at the distal tibia and fibula (white arrow) (A). Bone scintigraphy with ^{99} ^{m}Tc-methylene diphosphonate showed a marked increase in radioactivity around the ankle (black arrow) (B).

In accordance with the diagnosis of CRPS I accompanied by marked regional osteoporotic changes, oral administration of risedronate at 2.5 mg per day, the same dose used for the treatment of osteoporosis in Japan, was initiated to reduce the high bone turnover and ankle pain (VAS score of 59 out of 100). One month after the start of risedronate treatment, bone pain had fallen from a VAS score of 59 out of 100 to 18 out of 100, and we temporarily discontinued treatment at five months because of successful ankle pain

reduction and the presence of epigastric pain. After nine months (four months after the discontinuation of treatment), we resumed bisphosphonate treatment with oral alendronate at 35 mg per week and the ankle pain decreased from a VAS score of 18 out of 100 to 10 out of 100 at 15 months (Figure 2). Bone scintigraphy at 12 months showed a marked reduction in radioactivity to a level comparable to that in the normal, left ankle (Figure 3). In addition, the effect of bisphosphonate on bone pain relief correlated with a reduction in NTX level, from 37.6 to 12.9 at eight months. On the basis of these results, treatment was discontinued at 15 months, and ankle pain relief lasted for 32 months (Figure 2). At the latest examination at 32 months, our patient had almost no pain (VAS score of 9 out of 100) and radiographic findings revealed that the regional osteoporotic change in his ankle had returned to normal, and findings were equivalent to those for his left ankle (Figure 4).

A second 48-year-old Japanese man with CRPS was referred to our institute for treatment of severe right foot pain with a VAS score of 83 out of 100. About nine months earlier, he began to feel severe right foot pain without any trigger events. Although treatment, including physiotherapy and NSAID administration, was initiated in another clinic, the pain and swelling of his right foot progressively worsened, and he demonstrated gait disturbance. A physical examination revealed redness, swelling, and remarkable tenderness of his foot. Severe pain and hyperalgesia also resulted in the disturbance of weight-bearing. Radiographs showed regional osteoporotic changes in the phalanges, metatarsals, and tarsals of his right foot compared with his normal, left foot (Figure 5A). Reconstitution computed tomography also exhibited the extensive osteoporotic changes in his foot and ankle (Figure 5B). Bone scintigraphy with ^{99m}Tc-methylene diphosphonate revealed a marked increase in radioactivity in the bones of his foot (Figure 5C). These clinical findings were consistent with CRPS I according to the criteria [2] described for our first patient. Lumbar bone mineral density was 0.838 g/cm^2, which is more than 80% of the YAM. Laboratory tests showed an NTX of 48.6 nMBCE/mM·CR and normal values of ALP (242 U/L), serum calcium (9.6 mg/dL), serum phosphate (3.1 mg/dL), white blood cell count (7100/μL), and C-reactive protein (< 0.1 mg/dL).

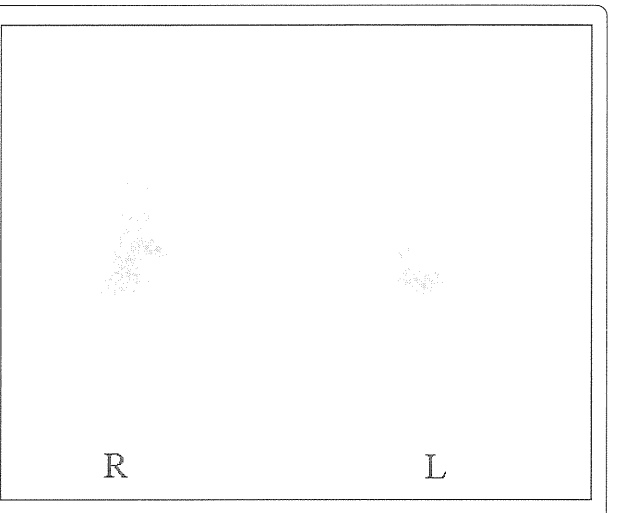


Figure 3 Bone scintigraphs of the both ankles after treatment. The previously increased radioactivity (Figure 1B) in the right ankle was markedly reduced, and findings were comparable to those of the normal, left ankle at 12 months after the start of bisphosphonate treatment.

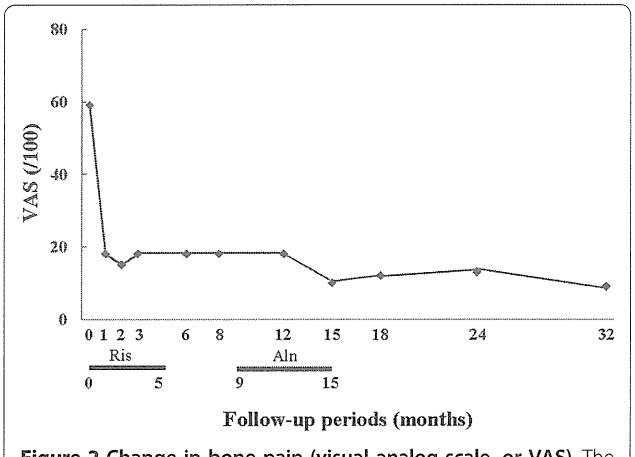


Figure 2 Change in bone pain (visual analog scale, or VAS). The reduction in VAS score after the oral administration of low doses of bisphosphonate. Aln, duration of treatment with alendronate at 35 mg per week; Ris, duration of treatment with risedronate at 2.5 mg per day; VAS, visual analog scale (/100 mm).

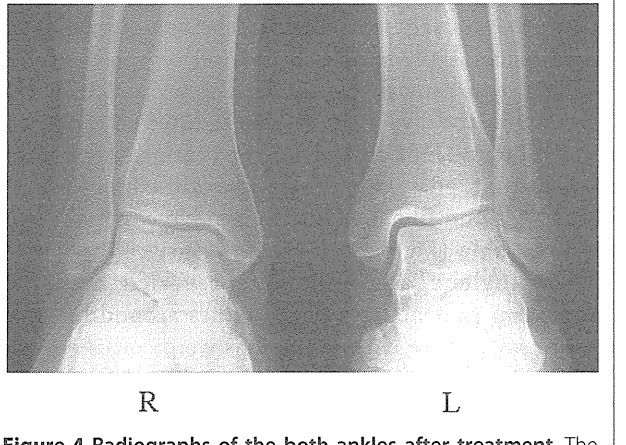


Figure 4 Radiographs of the both ankles after treatment. The regional osteoporotic change in the right ankle (Figure 1A) completely returned to normal, and findings were comparable to those of the left ankle at 32 months after the start of bisphosphonate treatment.

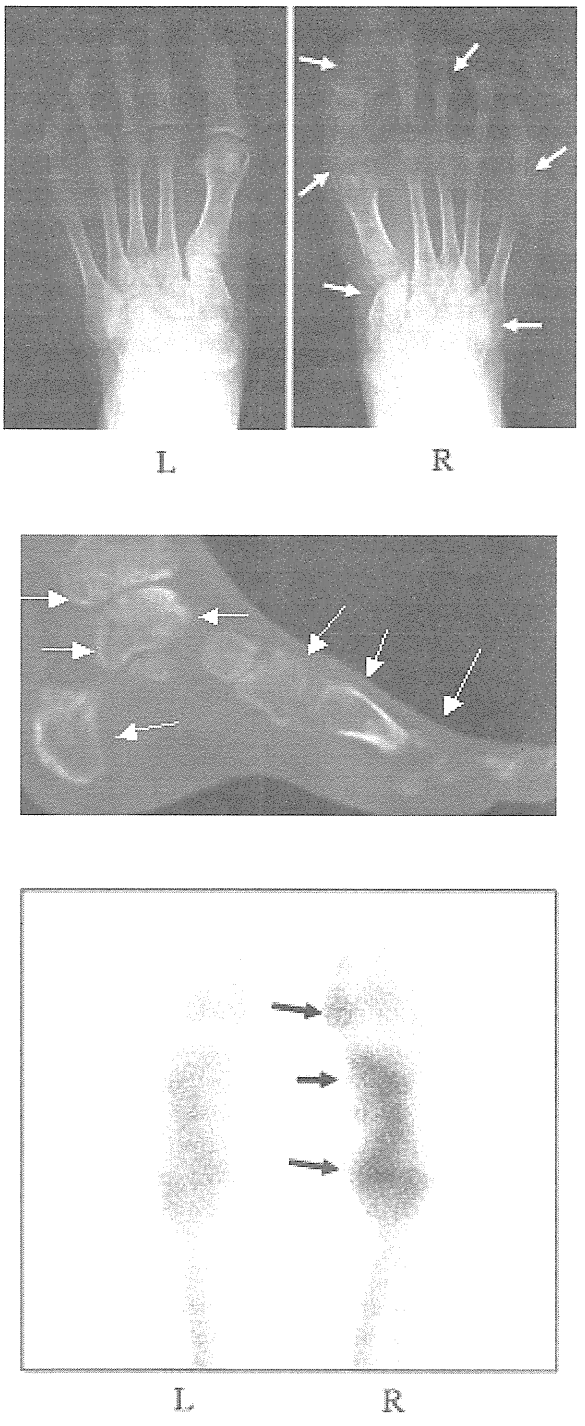


Figure 5 Radiograph (A), reconstitution computed tomography (CT) image (B), and scintigraph (C) of the both feet before treatment. The radiograph shows regional osteoporotic changes in the phalanges, metatarsals, and tarsals of the right foot compared with the normal, left foot (white arrow) (A). Reconstitution CT image exhibits the extensive osteoporotic changes in the foot and ankle (white arrow) (B). Bone scintigraphy with ^{99m}Tc-methylene diphosphonate shows a marked increase in radioactivity in the right foot (black arrow) (C).

In accordance with the diagnosis of CRPS I accompanied by marked regional osteoporotic findings together with the successful treatment of our first patient, weekly oral administration of alendronate at 35 mg per week, the same dose used for the treatment of osteoporosis in Japan, was initiated to reduce the high bone turnover and foot pain (VAS score of 83 out of 100). One month after the start of alendronate treatment, bone pain had fallen from a VAS score of 83 out of 100 to 30 out of 100 and was further reduced to 18 out of 100 at three months and 3 out of 100 at nine months. The treatment was discontinued at 15 months because of successful pain reduction, and the pain relief lasted for 30 months without further alendoronate administration (Figure 6). The bone pain relief correlated with a decrease in NTX values: 12.0 at 15 months and 14.0 at 24 months. Our patient rejected follow-up bone scintigraphy because he experienced no symptoms. At the latest examination at 30 months, he had no pain (VAS score of 0 out of 100) and the radiographic findings revealed marked improvement in regional osteoporotic changes (Figure 7).

Discussion

CRPS I is difficult to treat, despite the various methods that have been tried [3-5], and the therapeutic use of various drugs has been reported to be effective in some studies and useless in others [3,4,7]. Pathophysiologically, CRPS reveals enhanced regional bone resorption and high bone turnover, and so several reports have indicated that administration of bisphosphonate results in a significant reduction in pain [8-11,13,14]. However, in these studies, the method of administration was intravenous or in high oral doses (alendronate, 40 mg per day). Recent studies have shown that intravenous or high-dose bisphosphonate therapy increases the incidence of severe side effects, such as bisphosphonate-related osteonecrosis

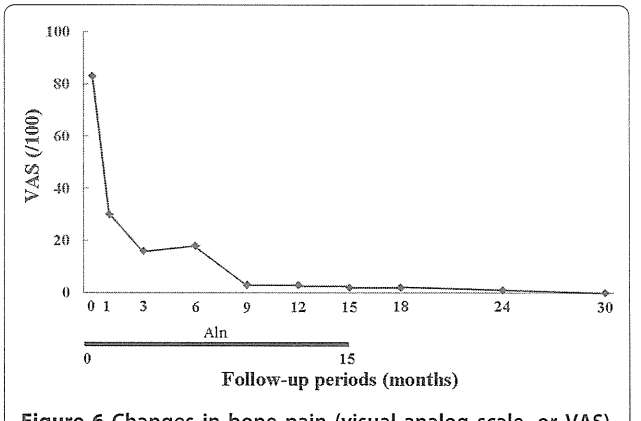


Figure 6 Changes in bone pain (visual analog scale, or VAS). The reduction in VAS score after the oral administration of low doses of bisphosphonate. Aln, duration of treatment with alendronate at 35 mg per week; VAS, visual analog scale (/100 mm).

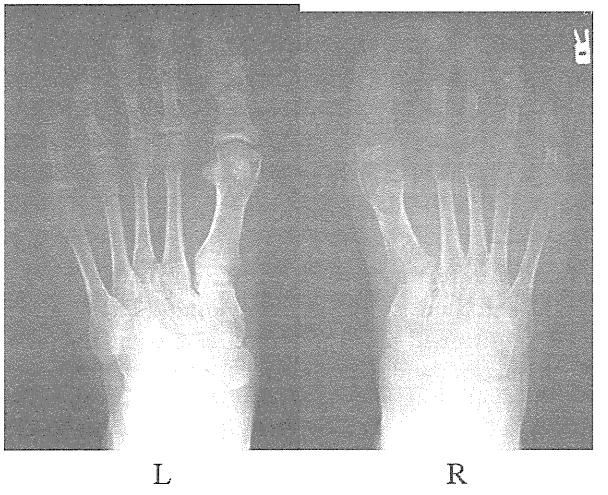


Figure 7 Radiographs of the both feet after treatment. The regional osteoporotic changes in the right foot (Figure 5A) were markedly improved at 32 months after the start of bisphosphonate treatment.

of the jaw [15] or severely suppressed bone turnover [16,17]. It was, therefore, considered ideal if low-dose bisphosphonate treatment could result in similar improvements in CRPS symptoms. In this report, we presented two patients who had CRPS I and who demonstrated marked pain relief and improvements in regional osteoporotic change in the foot or ankle as a result of the low-dose oral administration of bisphosphonate (risedronate at 2.5 mg per day or alendronate at 35 mg per week) at doses equivalent to those used for the treatment of osteoporosis in Japan. Also, in both cases, the ameliorative effects have lasted more than one year, even after the administration of bisphosphonate was discontinued. We administered the bisphosphonate as a daily risedronate or weekly alendronate dose, depending on epigastric symptoms and patient preference. To the best of our knowledge, few reports have indicated that a low dose of oral bisphosphonate has any efficacy in the treatment of CRPS I, particularly if the follow-up period after the discontinuation of treatment was more than one year.

The etiology of CRPS I varies, and several studies have indicated that most cases of CRPS I are caused by secondary etiologies such as trauma and diabetes [10,11]. Manicourt and colleagues [11] showed that traumatic events triggered CRPS I in most of their cases and that the pain associated with the disease was due not only to enhanced bone turnover but also to the production of proinflammatory cytokines and various neuropeptides from sustained peripheral nerve injury as a post-traumatic event [11,18,19]. The value of bisphosphonates in the treatment of CRPS I disease did not, therefore, seem great. However, in regard to the idiopathic cases of CRPS I presented here, bisphosphonate treatment markedly and rapidly improved the severe bone pain and afforded a concomitant reduction in bone turnover in the foot and ankle. It was previously recognized that bone disorders with increased osteoclastic bone resorption, such as Paget disease, are associated with bone pain [20], and the osteoclastic bone resorption was suggested to be critical to the pain, and the inflammation occurred adjacent to bone through an activation of the acid-sensing receptors through creation of acidosis by the osteoclasts [21]. In these cases, bisphosphonates, inhibitors of osteoclast activity, were shown to reduce bone pain. Thus, in our idiopathic cases, accelerated and enhanced bone resorption and turnover in the foot or ankle might have played a dominant pathophysiological role in the development of CRPS I rather than peripheral nerve disorder as a post-traumatic injury.

This report has a limitation. We cannot deny the possibility that the observed improvement of pain and osteoporotic changes was a consequence of spontaneous amelioration of the disease. However, in regard to the immediate improvement of pain and regional osteoporosis change after the initiation of bisphosphonate treatment and the ineffectiveness of the previous treatment (including physiotherapy and NSAID administration for about six months), the improvement could be considered the effect of bisphosphonate. Thus, we believe that low-dose oral administration of bisphosphonate is worth considering for the treatment of idiopathic CRPS I accompanied by high regional bone turnover.

Conclusions

In two patients with CRPS I, the oral administration of low-dose bisphosphonate resulted in an improvement in severe pain and regional osteoporotic findings in the foot or ankle. We speculate that a low dose of oral bisphosphonate might also be effective for the reduction in pain in cases of idiopathic CRPS I, particularly when accompanied by regional osteoporotic changes.

Consent

Written informed consent was obtained from the patients for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Abbreviations

ALP: alkaline phosphatase; CRPS: complex regional pain syndrome; CRPS I: complex regional pain syndrome type I; NSAID: nonsteroidal anti-inflammatory drug; NTX: N-telopeptides of type I collagen; VAS: visual analog scale; YAM: young adult mean.

Author details

[1]Department of Orthopedic Surgery, Sapporo Medical University School of Medicine, Sapporo 060-8543, Japan. [2]Kitago Orthopedic Clinic, Sapporo, Japan.

Authors' contributions
YA, JT, and TW performed the bisphosphonate treatment and several examinations of the patients and carried out the follow-up of the patients for more than 30 months. KI performed the bisphosphonate treatment and several examinations of the patients, carried out the follow-up of the patients for more than 30 months, conceived of the study, participated in its design and coordination, and helped to draft the manuscript. TY conceived of the study, participated in its design and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Received: 17 February 2011 Accepted: 4 August 2011
Published: 4 August 2011

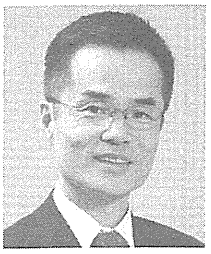
References

1. Veldman PH, Reynen HM, Arntz IE, Goris RJ: **Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients.** *Lancet* 1993, **342**:1012-1016.
2. Sumitani M, Shibata M, Sakaue G, Mashimo T, Japanese complex regional pain syndrome research group: **Development of comprehensive diagnostic criteria for complex regional pain syndrome in the Japanese population.** *Pain* 2010, **150**:243-249.
3. Bengtson K: **Physical modalities for complex regional pain syndrome.** *Hand Clin* 1997, **13**:443-454.
4. Stanton-Hicks M, Baron R, Boas R, Gordh T, Harden N, Hendler N, Koltzenburg M, Raj P, Wilder R: **Complex regional pain syndromes: guidelines for therapy.** *Clin J Pain* 1998, **14**:155-166.
5. Forouzanfar T, Koke AJ, van Kleef M, Weber WE: **Treatment of complex regional pain syndrome type I.** *Eur J Pain* 2002, **6**:105-122.
6. Doury P: **Algodystrophy: revlex sympathetic dystrophy syndrome.** *Clin Rheumatol* 1988, **7**:173-180.
7. Kozin F: **Reflex sympathetic dystrophy syndrome.** *Curr Opin Rheumatol* 1994, **6**:210-216.
8. Schott GD: **Bisphosphonate for pain relief in reflex sympathetic dystrophy.** *Lancet* 1997, **350**:1117.
9. Adami S, Fossaluzza V, Gatti D, Fracassi E, Braga V: **Bisphosphonate therapy of revlex sympathetic dystrophy syndrome.** *Ann Rheum Dis* 1997, **56**:201-204.
10. Kubalek I, Fain O, Paries J, Kettaneh A, Thomas M: **Treatment of reflex sympathetic dystrophy with pamidronate: 29 cases.** *Rheumatology* 2001, **40**:1394-1397.
11. Manicourt DH, Brasseur JP, Boutsen Y, Depreseux G, Devogelaer JP: **Role of alendronate in therapy for posttraumatic complex regional pain syndrome type I of the lower extremity.** *Arthritis Rheum* 2004, **50**:3690-3697.
12. McQuay HJ, Moore RA: **Methods of therapeutic trials.** In *Textbook of PAIN*.. 4 edition. Edited by: Wall PD, Melzack R. London: Churchill Livingstone; 1999:1125-1126.
13. Maillefert JF, Chatard C, Owen S, Peere T, Tavernier C, Tebib J: **Treatment of refractory reflex sympathetic dystrophy with pamidronate.** *Ann Rheum Dis* 1995, **54**:687.
14. Varenna M, Zucchi F, Ghiringhelli D, Binelli L, Bevilacqua M, Bettica P, Sinigaglia L: **Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome. A randomized double blind, placebo controlled study.** *J Rheumatol* 2000, **27**:1477-1483.
15. Colella G, Campisi G, Fusco V: **American association of oral and maxillofacial surgeons position paper: bisphosphonate-related osteonecrosis of the jaw-2009 update; the need to refine the BRONJ definition.** *J Oral Maxillofac Surg* 2009, **67**:2698-2699.
16. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY: **Severely suppressed bone turnover: a potential complication of alendronate therapy.** *J Clin Endocrinol Metab* 2005, **90**:1294-1301.
17. Lenart BA, Lorich DG, Lane JM: **Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate.** *N Engl J Med* 2008, **358**:1304-1306.
18. Bonabello A, Galmozzi MR, Canaparo R, Serpe L, Zara GP: **Long-term analgesic effect of clodoronate in rodents.** *Bone* 2003, **33**:567-574.
19. Janig W, Baron R: **Complex regional pain syndrome: mystery explained?** *Lancet Neurol* 2003, **2**:687-697.
20. Siris ES, Lyles KW, Singer FR, Meunier PJ: **Medical management of Paget's disease of bone: indications for treatment and review of current therapies.** *J Bone Miner Res* 2006, **21**:94-98.
21. Nagae M, Hiraga T, Wakabayashi H, Wang L, Iwata K, Yoneda T: **Osteoclasts play a part in pain due to the inflammation adjacent to bone.** *Bone* 2006, **39**:1107-1115.

doi:10.1186/1752-1947-5-349
Cite this article as: Abe *et al.*: Improvement of pain and regional osteoporotic changes in the foot and ankle by low-dose bisphosphonate therapy for complex regional pain syndrome type I: a case series. *Journal of Medical Case Reports* 2011 **5**:349.

原発性骨粗鬆症の治療

Treatment of primary osteoporosis



萩野　浩
Hiroshi HAGINO
鳥取大学医学部保健学科

◎骨粗鬆症は，骨強度が低下して骨折しやすい状態にある全身的な骨疾患で，骨脆弱化の進行には，主として骨吸収の亢進が関与する．骨粗鬆症の治療の目的は骨折の予防であり，すでに骨折を有する例ではあらたな骨折を防ぐことにある．骨粗鬆症の治療の三大柱には，運動療法，食事療法，薬物療法があげられる．食事療法はそれのみで骨量の増加や骨折予防が期待されるわけではなく，骨粗鬆症の基本治療に位置づけられる．運動療法によって骨折発生率が低減したとする報告はこれまでほとんどないが，骨密度を改善し，転倒を予防することから，骨折予防効果があると考えられている．薬物療法は高いエビデンスレベルの臨床研究により骨折抑制効果が確認されている．治療に用いられる薬剤は，その作用機序から骨吸収抑制薬と骨形成促進薬とに分類され，治療では骨吸収抑制薬が中心に使用される．骨折の予防には，さらに転倒予防，転倒時の衝撃緩衝材の使用が試みられる．

Key word：骨粗鬆症，骨吸収抑制薬，骨形成促進薬，衝撃緩衝材，骨折予防

骨粗鬆症は骨強度が低下して骨折しやすい状態にある全身的な骨疾患であり，臨床症状を有していなくても易骨折性が認められれば，骨粗鬆症と診断される．2000年にアメリカ国立衛生研究所(NIH)で開催されたコンセンサス会議で，骨粗鬆症は，「骨強度の低下を特徴とし，骨折のリスクが増大しやすくなる骨格疾患」と定義され，“骨強度”は骨密度と骨質の2つの要因からなり，骨密度は骨強度の約70%を説明するとされた．

骨粗鬆症は多因子疾患であり，遺伝的要因と生活習慣のような後天的な要因が発症に関与する．骨量が減少して骨脆弱性が亢進しても，骨折を有しない症例は無症状であるところから“沈黙の疾患”とよばれる．したがって，本症のおもな臨床症状は脆弱性骨折による疼痛と，骨折後の変形・機能障害である．

骨粗鬆症の病態

骨粗鬆症の治療を考えるうえでは，その病態を理解しておく必要がある．骨は1型コラーゲンを中心とした骨基質(類骨)にヒドロキシアパタイトが沈着して石灰化骨となる．骨粗鬆症は，骨の量的な減少がみられるが石灰化は正常で，この点で石灰化が障害されて類骨の割合が増加する骨軟化症やくる病とは区別される．

成長期に骨はカルシウムを蓄積し，急速に拡大する．ヒトでは20歳代までに人生で最大の骨量(最大骨量)に達する．この最大骨量獲得には，①遺伝的要因，②成長期の栄養・運動，③内分泌ホルモン，などが関与するため，種々の原因により最大骨量が低値となる可能性がある．最大骨量が低値であると，閉経後に生じる骨量減少により，早期に骨の脆弱性が増して，骨粗鬆症を発症する．

さらに，骨の成長が終了しても骨は生涯にわたって骨リモデリングとよばれる新陳代謝を繰り返す．リモデリングとは，マクロでの骨の形態は変化しないで，顕微鏡的なレベルでは，既存の古い骨が破骨細胞によって吸収され，その部位に骨芽細胞によって新しい骨が添加される変化を指す(図1)[1]．成長後にはさまざまな原因で骨形成と骨

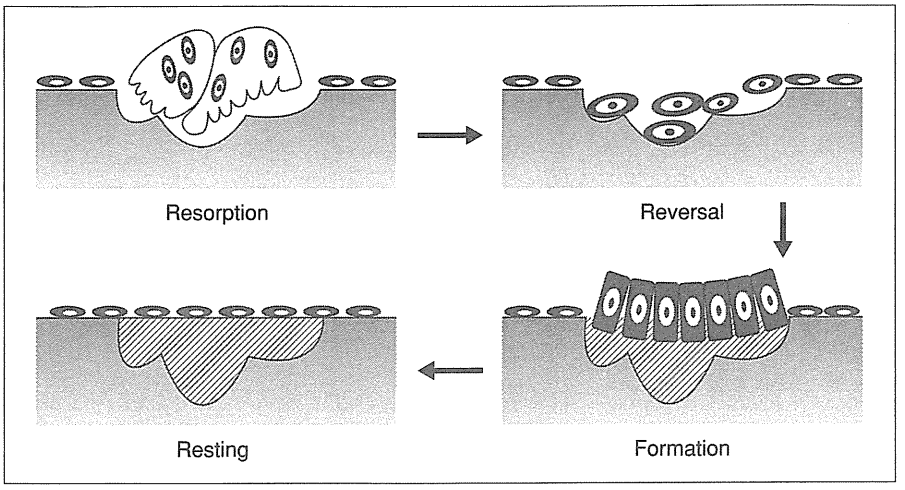


図 1　骨リモデリング[1)]
休止期にあった骨表面で破骨細胞が活性化され，骨吸収期となる(resorption)．その後，逆転期(reversal)，骨形成期(formation)を経て，ふたたび休止期となる．この一連の骨代謝が骨リモデリングであり，吸収された骨量と同じ量の骨形成が行われる(カップリング)．

吸収とにインバランスを生じ骨量が減少する[2)]．成人後の骨リモデリングにインバランスを生じるのはおもに閉経，加齢，運動不足が原因となる．女性ホルモンには破骨細胞の骨吸収を抑制する働きがあり，閉経による急激なホルモンレベルの低下により，骨吸収が亢進する．骨吸収の亢進に伴って骨形成も亢進するものの，形成が追いつかず，骨量減少をきたす．歩行や運動による骨へのメカニカルストレスは骨芽細胞の骨形成を促進し，骨量の維持・増加をもたらす．したがって，日常生活動作の障害や長期臥床，加齢に伴う運動量の低下は骨脆弱化を惹起する．

骨の強度には骨量のみではなく，骨質が関与することが強調されるようになっている．これは骨折のリスクが骨量だけでは説明できなくなったためである．たとえば，1990 年代はじめにアメリカで行われた骨粗鬆症治療薬フッ化ナトリウムの臨床試験では，高用量を用いると腰椎の骨密度が35%も増加するにもかかわらず，椎体骨折の発生頻度を低下させることはできず，四肢骨折の頻度を逆に増加させることが明らかとなった[3)]．この“骨質”には骨リモデリングが関与し，過剰な骨代謝回転の亢進あるいは低下によって骨質は劣化する(「サイドメモ」参照)．

骨粗鬆症治療の目的

骨粗鬆症は骨折を併発しなければ臨床症状を生じない．しかし，ひとたび骨折を併発すると，高齢者の移動能力をはじめとした生活機能が著しく障害されると同時に，あらたな骨折のリスクがきわめて高まる．したがって，骨粗鬆症の治療の目的は骨折の予防であり，すでに骨折を有する例ではあらたな骨折を防ぐことにある．

サイドメモ　リモデリング，骨質

リモデリング：リモデリングに要する時間は破骨細胞形成と骨吸収期が 10〜14 日，逆転相が 10 日，骨形成相が 90 日程度とされており，年間に 2〜10%の骨が更新される[2)]．

骨質：工学材料で“質”といえば材質を指すが，器官としての“骨”はけっして単一の材料でできあがっているわけではない．骨は約 70%のミネラルと約 30%の基質とからなるが，器官としての骨には，これに加えて各種の細胞があり，個体を支え強度を保つため，機能的な構造を形成して生体を維持している．そこで“骨質”は構造と材質とに分けて論じられている．この構造特性と材質特性のいずれにも骨リモデリングが関与し，過剰な骨代謝回転の亢進・低下によって骨質は劣化する．

このような観点から，骨粗鬆症の治療では骨代謝動態が改善したり骨密度が増加したりしても，骨折の予防効果がなければ，有効な治療法であると認められない．しかし，骨折は発生頻度が低いため，大規模臨床試験を実施しなければ骨折予防効果を証明することが困難である．そのため骨粗鬆症の治療の三大柱である運動療法，食事療法，薬物療法のうちで，高いエビデンスレベルの臨床研究により骨折抑制効果が確認されているのは薬物療法のみである．骨折の予防では，これらに加えて転倒予防，転倒時の衝撃緩衝材(ヒッププロテクターなど)の使用がある．

食事療法

骨粗鬆症の治療のための食事指導では，エネルギーおよび各栄養素がバランスよく摂取できたうえで，さらにカルシウムとビタミンD，ビタミンKなどの本疾患の治療に必要な栄養素を積極的に摂取させる[4]．高齢者で蛋白質摂取が不足している例では，適切な摂取量を指導する．

骨粗鬆症性骨折と食事に関するこれまでの報告によれば，カルシウム，ビタミンDがリスクを低減し，アルコール過剰摂取がリスクを上昇することが，高いエビデンスレベルで示されている[5]．また，果物・野菜，大豆製品，アルコールの適量摂取は骨折リスク低下の可能性が，食塩の過剰摂取，蛋白質摂取不足(高齢者)，蛋白質過剰摂取は骨折リスクを上昇させる可能性がある[5]．最近のわが国での調査結果では，閉経後骨粗鬆症例ではカルシウムとビタミンD摂取量は日本人平均値よりも高かった．しかし同時に，血清ビタミンD(25(OH)D_3)値は低値で，副甲状腺ホルモンもそれに伴い高値で，摂取量が厚生労働省の基準値を超えていても，なおビタミンD栄養状態が良好でないことも判明している[5]．

食事療法はそれのみで骨量の増加や骨折予防が期待されるわけではなく，骨粗鬆症の基本治療に位置づけられる．わが国のガイドラインの摂取目標量は，カルシウムは800 mg以上(食事で十分に摂取できない場合には1,000 mgのサプリメントを用いる)，ビタミンDは400～800 IU(10～20 μg)，ビタミンKは250～300 μgである[4]．

運動療法

これまでの臨床研究結果では，運動により非運動群に比較して骨密度が有意に維持・増加されることが明らかとなっている．1966～2000年までの45～70歳を対象とした90の研究から18の研究を抽出したシステマティックレビュー結果[6]によれば，有酸素運動，荷重運動，筋力増強運動のいずれも腰椎骨密度の維持・増加効果が認められる．また，ウォーキングは腰椎骨密度で1.3%，大腿骨近位部骨密度で0.92%の差が対照群との間でみられ，両部位の骨密度の増加に有効である．Martyn-Stら[7]は，メタアナリシスにより閉経後女性に対する筋力増強運動の効果を検証し，14論文では平均約10.5カ月の期間で腰椎の骨密度の有意な増加が得られることを示した．大腿骨近位部骨密度は11論文の解析結果では有意な維持・増加効果はなかったものの，ホルモン補充療法や骨吸収抑制薬を使用している患者を除外した8論文の解析ではその維持・増加傾向にあった．

骨折抑制効果が認められなければ骨粗鬆症の治療に適さないが，これまで運動療法によって骨折発生率が低減したとする報告は，小規模の前向き試験に限られる[8]．しかし運動療法により骨密度が改善し，後述のように転倒が予防されることから，運動療法には骨折予防効果があると考えられている．

高齢者に運動療法を実施する際には，持久力に個人差が大きく，心疾患，呼吸器疾患などの内科的合併症や，変形性膝関節症，腰痛性疾患などの運動器合併症の頻度が高いことを考慮する必要がある．各症例の運動機能障害に応じた運動療法を総合的に組み合わせて実施する．また，立位のバランスや起立歩行能力も損なわれている例では，体操療法，起立練習，水中運動，バランス練習などを中心とする．

薬物療法

骨粗鬆症の治療に用いられる薬剤は，その作用機序から骨吸収抑制薬と骨形成促進薬とに分類される．骨吸収抑制薬にはビスホスフォネート(アレンドロネート，リセドロネート，ミノドロネート，エチドロネート)，カルシトニン，選択的エストロ

表 1　骨粗鬆症治療薬の選択例

対象	薬剤選択例
骨折の既往を有する骨折リスクの高い例	アレンドロネート，リセドロネート，ミノドロネート，塩酸ラロキシフェン，バゼドキシフェン酢酸塩，テリパラチド
鎮痛作用を期待する例	カルシトニン製剤
更年期障害を有する例	女性ホルモン
カルシウム不足例	乳酸カルシウム，活性型ビタミン D_3
閉経前症例	活性型ビタミン D_3製剤，ビタミン K_2製剤

ゲン受容体モジュレーター(selective estrogen receptor modulator：SERM，塩酸ラロキシフェン，バゼドキシフェン酢酸塩)，エストロゲンが，骨形成促進薬には副甲状腺ホルモン(テリパラチド)が分類される．活性型ビタミン D_3およびビタミン K_2は骨吸収抑制薬，骨形成促進薬のいずれにも分類されない薬剤である．近年ではその基礎的・臨床的知見から活性型ビタミン D_3は骨吸収抑制薬に，ビタミン K_2は骨形成促進薬に分類される傾向にある．現時点ではわが国の骨粗鬆症治療薬は骨吸収抑制薬が中心である．

ほとんどの骨粗鬆症治療薬は経口薬であり，カルシトニン製剤とテリパラチドが注射製剤である．

ビスホスフォネート薬は消化管から吸収されると速やかに骨に沈着し，一度吸収されたビスホスフォネートは服薬が一定期間行われないで血中濃度が低下しても，骨中に沈着してその有効性を発揮する．そこで服薬間隔を延長することが可能なことから，週1回製剤が開発されている．また，ダイドロネルは2週間服薬，10〜12週間休薬を1クールとした周期的間欠投与が行われる．カルシトニン注射製剤は週1回または週2回投与である．

『骨粗鬆症の予防と治療ガイドライン(2006年版)』[4]では掲載，治療効果に従って各骨粗鬆症治療薬の推奨グレードが示された．この推奨グレードに従った実際の薬剤選択では，骨折の既往を有する骨折リスクの高い例では，窒素含有ビスホスフォネート(アレンドロネート，リセドロネート，ミノドロネート)，SERM(塩酸ラロキシフェン，バゼドキシフェン酢酸塩)が第一選択となる(表1)．抗テリパラチドも骨折リスクの高い例が治療対象となる．

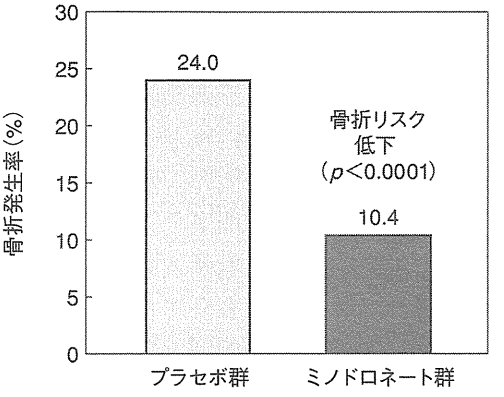


図 2　ミノドロネートの椎体骨折抑制効果[10]
椎体骨折発生率がプラセボ群で24.0%であったのに対し，ミノドロネート群では10.4%で，相対危険度は0.411(95%信頼区間：0.267-0.634)と，59%のリスク低下が示された．

窒素含有ビスホスフォネートのうち，ミノドロネートはわが国で開発され，骨粗鬆症治療薬として認可されたはじめての国産のビスホスフォネートである．2009年，本剤の投与による骨量増加がアレンドロネートと同程度であり，骨吸収マーカーの推移をアレンドロネート群と比較すると，有意にその改善効果が大きく，治療開始後4週で40%以上の低下が報告された[9]．また，骨折予防効果に関して674例の原発性骨粗鬆症患者(平均71歳)を対象に，ミノドロネートとプラセボを比較した2年間にわたる二重盲検比較試験の結果が示され[10]，椎体骨折発生率がプラセボ群で24.0%であったのに対し，ミノドロネート群では10.4%，相対危険度は0.411(95%信頼区間：0.267-0.634)と，59%のリスク低下が示された(図2)．さらに，この骨折リスクの低減は75歳未満の前期高齢者と75歳以上の後期高齢者とで同様であることも最近，報告された．

さらにあらたな骨吸収抑制薬として，抗ランク

ル抗体(デノスマブ)が開発され，2009年，その臨床成績が明らかとなった[11]．半年に一度の60 mgの皮下注射によって，椎体骨折のリスクを68%，大腿骨近位部骨折のリスクを40%，いずれも有意に低下した．

転倒予防とヒッププロテクター

骨粗鬆症治療の目的は“骨折の予防”である．骨折予防には骨粗鬆症の治療，すなわち骨脆弱性の改善のみではなく，転倒防止があげられる．転倒防止のためには，まず転倒リスクと危険因子の評価を行った後，可能な危険因子の改善に取り組む必要がある．これまでの介入研究から，個別の評価と包括的な介入が転倒率を低下させることが明らかになっている[12]．転倒防止のための運動療法では，筋力増強運動とともにバランス訓練が重要である．また，施設入所例でも個別のリスクアセスメント，ケアプラン作成と同時に，多職種連携，薬剤調整，栄養改善，環境調整，職員教育などの包括的介入によって転倒発生率が低減する[13]．

ヒッププロテクターは転倒時に生じる大腿骨近位部への衝撃を和らげるために，衝撃緩衝材が下着に装着されているものである．1993年にその有意な骨折予防効果が報告されて以来，注目されるに至った．しかし，左右片側に装着した臨床試験結果では，装着側のほうが逆に骨折発生率が高く[14]，その骨折予防効果についてはかならずしも一定の結果が得られていない．これは，調査にあたって在宅の高齢者を対象としたか施設入所者を対象としたか，どの程度リスクの高い高齢者を対象としたかで結果が異なるためである．在宅高齢者では継続率が低く効果を得にくいため，施設入所者でスタッフが十分に有用性を理解して装着継続率を高めると，その骨折予防効果が得られる．施設入所者のなかでも骨折リスクの高い例（高頻度転倒例，やせた症例）を対象にした場合には有効である[15]．

おわりに

ロコモティブシンドロームは運動器疾患が原因で介護に至るリスクの高い症候群であり，疾患の重複はさらにリスクを高める．骨粗鬆症は骨折を生じていなければ臨床症状に乏しいが，ひとたび骨折が起こると，さらに骨折リスクが上昇し，骨折が骨折を招来する“負の連鎖”に陥ることとなる．この連鎖を断ち切るために，ロコモティブシンドロームの予防，早期発見・改善が大切である．

文献

1) Dempster, D. W.：Bone remodeling. *In*：Osteoporosis(ed. by Riggs, B. L.). Lippincott-Ravan, Philadelphia, 1995, p.67-91.
2) Fleish, H.(森井浩世監訳)：ビスホスホネートと骨疾患．医薬ジャーナル社，2000.
3) Riggs, B. L. et al.：Clinical trial of fluoride therapy in postmenopausal osteoporotic women：Extended observations and additional analysis. *J. Bone Miner. Res.*, **9**：265-275, 1994.
4) 折茂　肇：骨粗鬆症の予防と治療ガイドライン2006年版．ライフサイエンス出版，2007.
5) 広田孝子：骨粗鬆症患者のカルシウムとビタミンDの栄養状態と骨代謝．*Osteoporos. Jpn.*, **16**：165-169, 2008.
6) Bonaiuti, D. et al.：Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database Syst. Rev.*, CD000333, 2002.
7) Martyn-St, J. M. et al.：High-intensity resistance training and postmenopausal bone loss：a meta-analysis. *Osteoporos. Int.*, **17**：1225-1240, 2006.
8) Sinaki, M. et al.：Stronger back muscles reduce the incidence of vertebral fractures：a prospective 10 year follow-up of postmenopausal women. *Bone*, **30**：836-841, 2002.
9) Hagino, H. et al.：A double-blinded head-to-head trial of minodronate and alendronate in women with postmenopausal osteoporosis. *Bone*, **44**：1078-1084, 2009.
10) Matsumoto, T. et al.：Effect of daily oral minodronate on vertebral fractures in Japanese postmenopausal women with established osteoporosis：a randomized placebo-controlled double-blind study. *Osteoporos. Int.*, **20**：1429-1437, 2009.
11) Cummings, S. R. et al.：Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N. Engl. J. Med.*, **361**：756-765, 2009.
12) Gillespie, L. D. et al.：Interventions for preventing falls in older people living in the community. *Cochrane Database Syst. Rev.*, CD007146, 2009.
13) Cameron, I. D. et al.：Interventions for preventing falls in older people in nursing care facilities and hospitals. *Cochrane Database Syst. Rev.*, CD005465, 2010.
14) Kiel, D. P. et al.：Efficacy of a hip protector to prevent hip fracture in nursing home residents：the HIP PRO randomized controlled trial. *JAMA*, **298**：413-422, 2007.
15) Koike, T. et al.：External hip protectors are effective for the elderly with higher-than-average risk factors for hip fractures. *Osteoporos. Int.*, **20**：1613-1620, 2009.