学位論文

Five-Year Experience with Risedoronate Therapy for Patients with Increased Fracture Risk: A Practice-Based Observational Study

（骨折リスクが高い患者を対象としたリセドロネートの5年間の治療成績
－実臨床下における観察研究－）

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Regular Article

Five-Year Experience with Risedronate Therapy for Patients with Increased Fracture Risk: A Practice-Based Observational Study

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The purpose of this practice-based observational study was to examine the effects of long-term treatment with risedronate in patients with an increased fracture risk. Seventy patients (4 men and 66 postmenopausal women; mean age, 68.0 years) with osteoporosis or osteopenia and clinical risk factors for fractures were treated with risedronate at either 2.5 mg/d or 17.5 mg/week for 5 years. The bone mineral density (BMD) of the lumbar spine and proximal femur, and the structural geometric parameters of the proximal femur were evaluated by dual-energy X-ray absorptiometry with advanced hip assessment software at baseline and after each year of treatment. The lumbar spine BMD rapidly increased during the first year of the treatment and steadily increased throughout the 5-year treatment period. The BMD of the femoral neck and total hip also significantly increased during the first 3 and 2 years of treatment, respectively, then gradually declined and reached the baseline level after 5 years of treatment. The cross-sectional moment of inertia, cross-sectional area, and mean width of the femoral neck region of interest significantly increased during the first 2 years, and these increases were maintained throughout the 5-year treatment period. The femur strength index and section modulus also significantly increased following time courses similar to those of the above three parameters. These results suggest that risedronate produced both a sustained increase in the lumbar spine BMD and improvement in the femoral structural geometric parameters for 5 years of treatment.

Key words risedronate; geometry; bone mineral density; advanced hip assessment; femur strength index

Osteoporosis is a skeletal disease characterized by a decrease in bone strength and is associated with an increased fracture risk.[1)] Bone strength depends on two factors: bone mineral density (BMD) and bone quality. Bone quality is determined by both structural and material factors; structural factors include the macroscopic structure of cancellous bone and the porosity of cortical bone, whereas material factors include the extent of calcification, crystal size, matrix content, and microdamage.[1)]

Clinical assessment of bone geometry and microstructure has recently become possible because of marked progress in imaging technology. Software for advanced hip assessment (AHA) installed in dual-energy X-ray absorptiometry (DXA) systems is now widely used to noninvasively determine the structural geometric parameters of the proximal femur.[2,3)] These structural parameters include the cross-sectional moment of inertia (CSMI) and cross-sectional area (CSA), from which the femur strength index (FSI) can be calculated. The FSI has predictive power for fracture risks in patients along with the BMD,[2,3)] and the FSI obtained by DXA with AHA is reportedly well correlated with that obtained by quantitative computed tomography (QCT).[4,5)]

Risedronate has been widely used as a first-line drug in the treatment of osteoporosis. Current evidence based strictly on the principles of evidence-based medicine suggests high antifracture efficacy and safety of risedronate in postmenopausal women and men with osteoporosis.[6–10)] We previously reported that 1 year of risedronate therapy significantly increased the BMD of the lumbar spine and femoral neck and improved geometric parameters including the CSMI and CSA.[11)] We also reported that 3 years of risedronate therapy maintained or attenuated these improvements in the BMD, CSMI, and CSA.[12)] However, very few studies have been performed in which the long-term effects of risedronate were evaluated using DXA incorporated with femoral geometric parameters. The purpose of this study was to investigate the effects of 5-year risedronate treatment on the AHA parameters of the proximal femur as well as the BMD of the proximal femur and lumbar spine in patients with an increased risk of fractures.

SUBJECTS AND METHODS

Subjects In our outpatient clinic (Takakuwa Orthopaedic Nagayama Clinic), risedronate was used as a first-line drug for treatment of men and postmenopausal women with osteoporosis or osteopenia and a clinical risk of fractures starting in July 2005. According to the Japanese diagnostic criteria,[13,14)] patients with a BMD of $<70\%$ of the young adult mean (YAM) or 70–80% of the YAM along with a history of osteoporotic fractures were diagnosed with osteoporosis. Lumbar spine BMD was used to diagnose osteoporosis or osteopenia. The clinical risk factors for fractures included current smoking, a maternal history of hip fractures, alcohol consumption of >2 units daily, age of >75 years, leanness (body mass index of $\leq 18.5\,kg/m^2$), and a history of steroid use. Of 255 patients treated with risedronate (2.5 mg/d or 17.5 mg/week) for 5 years, 181 patients with data available from the start of risedronate therapy were analyzed. Therapy with daily risedronate was initiated for all patients and continued until July 2008. When weekly risedronate became available after July 2008, the therapy was switched to weekly risedronate for all patients. At 60 months (5 years), data were available for 70

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patients. The inclusion criteria were men and postmenopausal women with osteoporosis or osteopenia with at least one clinical risk factor for fractures at the start of treatment. The exclusion criteria were a history of reflux esophagitis, gastric or duodenal ulcers, gastrectomy, or bone disease such as primary hyperparathyroidism, hyperthyroidism, Cushing syndrome, multiple myeloma, rheumatoid arthritis, or osteogenesis imperfecta. Data presentation in this article was approved by the Ethics Committee of Takakuwa Orthopaedic Nagayama Clinic.

Measurement of BMD and Proximal Femur Structural Geometric Parameters The BMD of the lumbar spine (L1–L4) and left and right proximal femur (neck, trochanter, and total) was measured by DXA with a Prodigy Advance device (GE Healthcare, Madison, WI, U.S.A.). The hip axis length (HAL, mm), cross-sectional moment of inertia (CSMI, mm^4), cross-sectional area (CSA, mm^2), mean femoral neck width (d3, mm), and femoral strength index (FSI) were assessed using software for AHA incorporated into the DXA system[7,8] (Fig. 1). The CSA was defined as the surface area of bone in a cross-section after excluding soft tissue (marrow) and was derived from the bone mass profile. The CSA is an index of resistance to force directed along the long axis of a bone. The CSMI was calculated as the integral of the bone mass profile across a bone weighted by the square of the distance from the center of gravity. The FSI was defined as the ratio of the estimated compressive yield strength of the femoral neck to the expected compressive stress applied by falling on the greater trochanter. Thus, FSI=strength/stress, where strength=185–0.34×(age−45) for patients aged >45 years and strength or 185 for those aged ≤ 45 years, and stress=moment×y/CSMI+force/CSA. In the following equations, moment=d1×8.25×weight×9.8 (height/170)$^{1/2}$×cos(180−θ) and force=8.25×weight×9.8 (height/170)$^{1/2}$×sin(180−θ), d1=distance (mm) along the neck axis from the center of the femoral head to the section of minimum CSMI, y=distance (mm) from the centroid to the upper neck margin along of the section of minimum CSMI, and θ=angle of the intersection between the neck and shaft axis. The section modulus (SM, mm^3), an index of bending strength, was derived as the CSMI divided by y (distance from the centroid to the upper neck margin along of the section of minimum CSMI). The buckling ratio (BR), an index of cortical stability under compressive loads, was calculated from CSMI/SM/lower neck cortical width (mm) at the same section of the CSMI. As the FSI increases, the risk of a hip fracture owing to a fall on the greater trochanter decreases.[2,3] Likewise, as the SM increases, the risk of a hip fracture decreases.[15] Conversely, if the BR increases, the risk of a hip fracture also increases.[15] Thus, AHA-based analysis can be employed to assess the structural geometry in terms of bone quality.

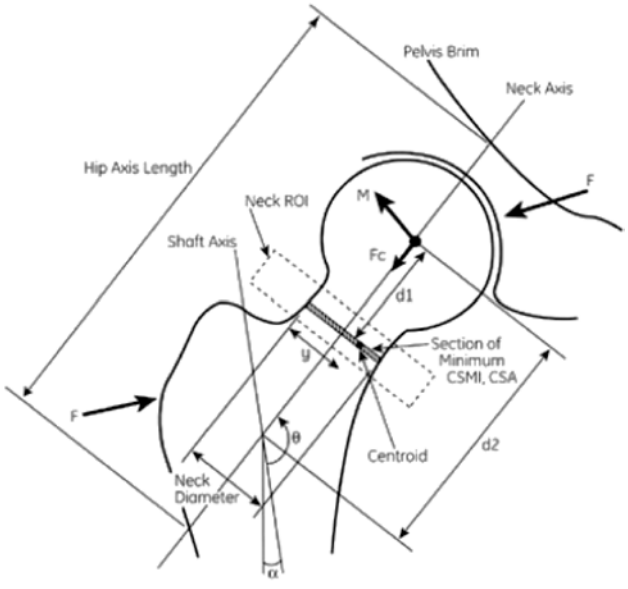

Fig. 1. Femur Geometry Showing the Parameters Used for Analysis of Femoral Strength by Advanced Hip Assessment (AHA)

CSMI, cross-sectional moment of inertia (mm^4); CSA, cross-sectional area (mm^2); d1, distance from the center of the femoral head to the CSMI (mm); d2, distance from the center of the femoral head to the shaft axis (mm); d3, mean neck width in the femoral neck region of interest (ROI); F, fall force; Fc, compressive force; M, bending force; y, distance from the center of gravity to the superior margin of the femoral neck (mm); a, angle between the shaft axis and the femoral neck axis.

Statistical Analysis Data are expressed as mean±standard deviation (S.D.). The paired t-test was used to compare BMD and AHA parameters between baseline and time points of 1, 2, 3, 4, and 5 years. All statistical analyses were performed using SAS Release 9.1 TSIM3 (SAS Institute, Cary, NC, U.S.A.). A significance level of $p<0.05$ was used for all comparisons.

RESULTS

Characteristics of Study Subjects The demographic characteristics of the patients are summarized in Table 1. Of the 181 patients who were available for analysis at the start of the study, 9 were men and 172 were women. Their mean (S.D.) age was 68.1 (10.0) years (range, 24–90), mean (S.D.) height was 148.7 (6.9) cm (range, 133.4–163.0 cm), and mean (S.D.) body weight was 50.9 (8.9) kg (range, 32.0–77.5 kg). The number of data available for each item at each point of measurement varied as shown in Table 2. As previously reported,[12] early study discontinuation (within 4 months) of up to 20% was because of adverse effects such as gastrointestinal

Table 1. Demographic Characteristics of Patients

Characteristics	Baseline	60 months
Number of patients, *n*	181	70
Male, *n* (%)	9 (5.0)	4 (5.7)
Female, *n* (%)	172 (95.0)	66 (94.3)
Age, years		
≤ 64, *n* (%)	65 (35.9)	20 (28.6)
65–69, *n* (%)	35 (19.3)	20 (28.6)
70–74, *n* (%)	30 (16.6)	12 (17.1)
≥ 75, *n* (%)	51 (28.2)	18 (25.7)
Mean±S.D.	68.1±10.0	68.0±8.3
Range	24–90	45–86
Height (cm)		
Mean±S.D.	148.7±6.9	148.4±6.8
Range	133.4–163.0	133.5–161.5
Body weight (kg)		
Mean±S.D.	50.9±8.9	50.1±9.3
Range	32.0–77.5	32.0–77.0

S.D.: standard deviation.

Table 2. Changes in Assessed Parameters

Parameters			Baseline		12 months		24 months		36 months		48 months		60 months	
Spine	BMD	L1–L4	(181)	0.871±0.130	(163)	0.904±0.136***	(126)	0.914±0.127***	(101)	0.902±0.140***	(75)	0.910±0.157***	(58)	0.907±0.172***
		L2–L4	(181)	0.894±0.138	(163)	0.930±0.146***	(126)	0.939±0.139***	(101)	0.928±0.148***	(82)	0.934±0.162***	(70)	0.939±0.179***
	YAM	L1–L4	(181)	77.8±11.2	(163)	80.8±11.8***	(126)	81.5±11.0***	(101)	80.5±12.1***	(75)	81.2±13.5***	(58)	81.4±15.6***
		L2–L4	(181)	74.8±11.2	(163)	77.7±11.8***	(126)	78.4±11.2***	(101)	77.5±12.0***	(82)	78.0±13.1***	(70)	77.9±14.9***
Femur (right)	BMD	Neck	(180)	0.703±0.088	(162)	0.706±0.095*	(125)	0.709±0.089**	(100)	0.709±0.089***	(81)	0.696±0.098	(70)	0.694±0.093
		Total	(180)	0.751±0.096	(162)	0.757±0.102***	(125)	0.764±0.100***	(100)	0.758±0.106†	(81)	0.752±0.105	(70)	0.737±0.096*
	YAM	Neck	(180)	77.9±9.8	(162)	78.2±10.5*	(125)	78.5±9.8**	(100)	78.5±9.9***	(81)	77.1±10.9	(70)	76.9±10.4
		Total	(180)	80.4±10.3	(162)	81.0±10.9***	(125)	81.8±10.8***	(100)	81.1±11.3†	(81)	80.5±11.3	(70)	78.9±10.2*
	AHA	HAL	(180)	102.1±6.3	(162)	101.0±6.6***	(125)	101.3±6.6***	(98)	101.0±6.3***	(81)	101.2±6.3*	(70)	101.3±6.4
		CSMI	(180)	6202.9±2073.6	(162)	6562.6±2194.9***	(125)	6889.4±2113.0***	(100)	6737.5±1976.5***	(81)	6576.1±2059.9*	(70)	6540.4±2140.8**
		CSA	(180)	98.2±14.6	(162)	100.7±16.0***	(125)	102.9±15.8***	(100)	101.4±15.7***	(81)	99.0±16.8†	(70)	99.1±15.8*
		d3	(180)	31.1±2.8	(162)	31.7±3.0***	(125)	32.1±2.7***	(100)	32.0±3.0***	(81)	31.6±2.6**	(70)	31.7±3.0***
		SI	(180)	1.48±0.41	(162)	1.58±0.48***	(125)	1.62±0.44***	(100)	1.66±0.42***	(81)	1.60±0.40**	(70)	1.56±0.41**
		SM	(179)	389.2±102.4	(162)	405.0±104.5***	(125)	421.1±100.1***	(100)	415.3±93.5***	(81)	409.9±104.2*	(69)	404.5±103.7**
		BR	(176)	4.19±1.88	(155)	4.53±2.36	(120)	4.41±1.84*	(97)	4.23±1.76	(72)	4.32±2.98	(65)	4.48±1.94
Femur (left)	BMD	Neck	(177)	0.701±0.089	(159)	0.703±0.095*	(122)	0.704±0.093*	(97)	0.702±0.093**	(79)	0.691±0.093	(67)	0.686±0.092
		Total	(177)	0.747±0.096	(159)	0.753±0.104***	(122)	0.756±0.103***	(97)	0.745±0.103	(79)	0.742±0.102	(67)	0.732±0.093
	YAM	Neck	(177)	77.6±9.8	(159)	77.9±10.6*	(122)	77.9±10.3*	(97)	77.8±10.4**	(79)	76.6±10.4	(67)	76.0±10.2
		Total	(177)	80.0±10.3	(159)	80.6±11.1***	(122)	80.9±11.0***	(97)	79.8±11.0	(79)	79.4±10.9	(67)	78.3±10.0
	AHA	HAL	(176)	101.0±6.3	(158)	100.1±6.8***	(122)	100.0±6.6***	(97)	99.7±7.1***	(79)	100.0±7.1*	(67)	99.6±6.9*
		CSMI	(177)	6108.9±1972.5	(159)	6441.2±1889.8***	(122)	6788.2±2238.6***	(97)	6476.9±1827.0***	(79)	6366.7±1924.2**	(67)	6331.7±1857.2***
		CSA	(177)	97.6±15.1	(159)	99.7±15.9***	(122)	100.9±16.3***	(97)	99.5±15.4***	(79)	99.0±16.1**	(67)	97.3±14.1*
		d3	(177)	31.0±2.6	(159)	31.6±2.8***	(122)	32.2±3.3***	(97)	31.9±2.8***	(79)	31.4±2.7***	(67)	31.6±2.8***
		SI	(177)	1.49±0.39	(159)	1.58±0.41**	(122)	1.66±0.51***	(97)	1.65±0.38***	(79)	1.68±0.46***	(67)	1.59±0.39***
		SM	(176)	383.5±97.3	(159)	395.8±94.1***	(122)	409.4±105.9***	(97)	395.8±89.2***	(79)	395.8±97.7**	(66)	390.6±90.2***
		BR	(173)	4.38±1.81	(153)	4.39±2.32	(116)	4.24±1.99	(94)	4.27±2.15	(76)	4.10±1.89	(59)	4.61±1.87

Data are expressed as mean±standard deviation. The numbers in parentheses are the numbers of patients assessed. The paired *t*-test was used to compare parameters among time points. Paired *t*-test: $^{\dagger}p<0.1$, $*p<0.05$, $**p<0.01$, $***p<0.001$. AHA, advanced hip assessment; BMD, bone mineral density (g/cm^2); BR, buckling ratio; CSA, cross-sectional area (mm^2); CSMI, cross-sectional moment of inertia (mm^4); d3, mean neck width in the femoral neck region of interest (mm); HAL, hip axis length (mm); SI, strength index; SM, section modulus (mm^3); YAM, young adult mean.

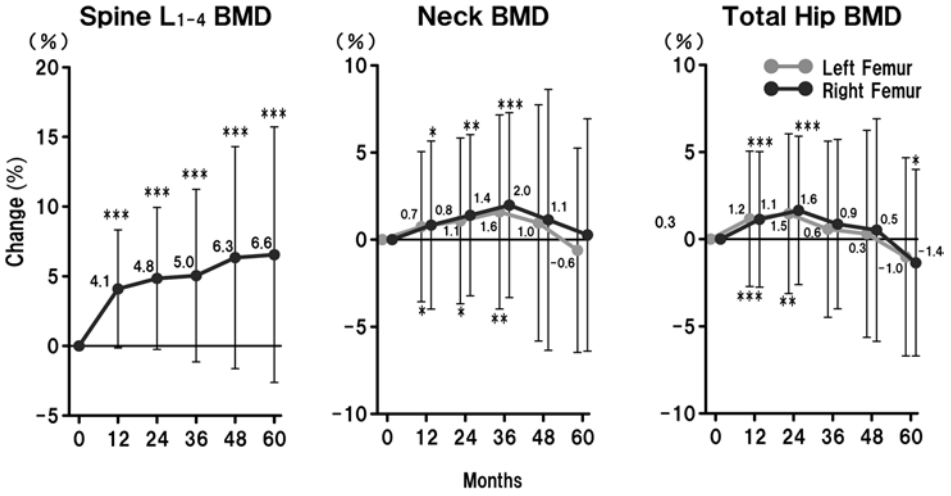

Fig. 2. Percent Changes in Bone Mineral Density (BMD) of the Lumbar Spine, Femoral Neck, and Total Hip

Data are expressed as mean±standard deviation. The paired *t*-test was used to compare parameters among time points. *$p<0.05$, **$p<0.01$, ***$p<0.001$.

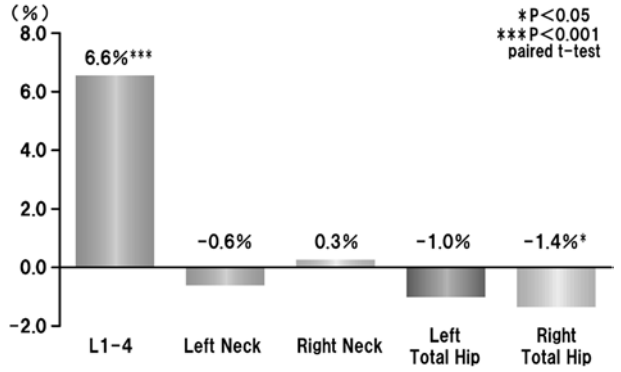

Fig. 3. Changes in Bone Mineral Density (BMD) from Baseline after 60 Months of Treatment

Each column represents the mean percent change. The paired *t*-test was used to compare the 60-month data and the baseline data. *$p<0.05$, ***$p<0.001$.

symptoms, diarrhea, and constipation; a high discontinuation rate thereafter was mainly attributable to non-compliance, fear of osteonecrosis of the jaw (ONJ) after tooth extraction, and loss to follow-up.

Changes in BMD Changes in BMD during the treatment are summarized in Table 2 and Fig. 2. The lumbar spine BMD significantly increased during the first year of treatment and continued to increase thereafter throughout the 5 years. The mean increases from baseline after 1, 2, 3, 4, and 5 years of treatment were 4.08%, 4.85%, 5.04%, 6.34%, and 6.55%, respectively. However, there were no significant differences among the data of these time points. The mean BMD of the right femoral neck increased significantly from baseline during the first 3 years (0.83%, 1.40%, and 1.97% after 1, 2, and 3 years of treatment, respectively), declined to 1.13% after 4 years, and reached the baseline level at 5 years. Similar results were obtained for the left femoral neck BMD. The mean BMD of the right total hip also significantly increased from baseline during the first 2 years (1.14% and 1.64% after 1 and 2 years of treatment, respectively); the increase declined to 0.85%, 1.51%, and −1.37% after 3, 4, and 5 years, respectively. The decrease after 5 years was statistically significant. The mean BMD of the left total hip followed a time course similar to that of the right total hip in that it significantly increased from baseline during the first 2 years (1.17% and 1.45% after 1 and 2 years, respectively), then declined to 0.57%, 0.30%, and −1.02% after 3, 4, and 5 years, respectively, although the BMD after 5 years was not significantly different from baseline. As shown in Fig. 3, the mean lumbar spine BMD increased by 6.6% at 5 years, whereas the BMD of the femoral neck and total hip did not differ from baseline, with the exception of the right total hip. The numerical data are summarized in Table 2.

Changes in AHA Figure 4 depicts the changes in the CSMI, CSA, and d3. These parameters significantly increased from baseline throughout the 5 years of treatment. As shown in Fig. 5 and Table 2, the FSI significantly increased from baseline throughout the 5-year treatment, suggesting a decreased fracture risk in a fall. Similarly, the SM significantly increased from baseline throughout the 5-year treatment. In contrast, the BR of the femur did not show clinically significant changes during the treatment period (Fig. 6, Table 2).

Adverse Events No serious adverse events, such as ONJ or femoral diaphysis atypical fractures, occurred in the present study, although such events have been reported in other studies.[16,17]

DISCUSSION

This practice-based observational study was conducted to examine the long-term effects of risedronate on the BMD and structural geometry of the femur in patients with osteoporosis or osteopenia and clinical risk factors for fractures. The BMD of the lumbar spine significantly increased from baseline during the 5-year treatment period. The BMD of the femoral neck and total hip also significantly increased from baseline, but declined after 3 and 2 years of treatment, respectively, and returned to the baseline levels after 4 and 3 years of treatment, respectively. Unlike the changes in BMD, the significant increases in the femoral geometric parameters (CSMI, CSA, and d3) and the FSI and SM of femur secondary to risedronate treatment were maintained throughout the 5 years. However, the BR of the femur poorly responded to risedronate and remained at the baseline level throughout the 5-years.

A multicenter, randomized, double-blind controlled trial

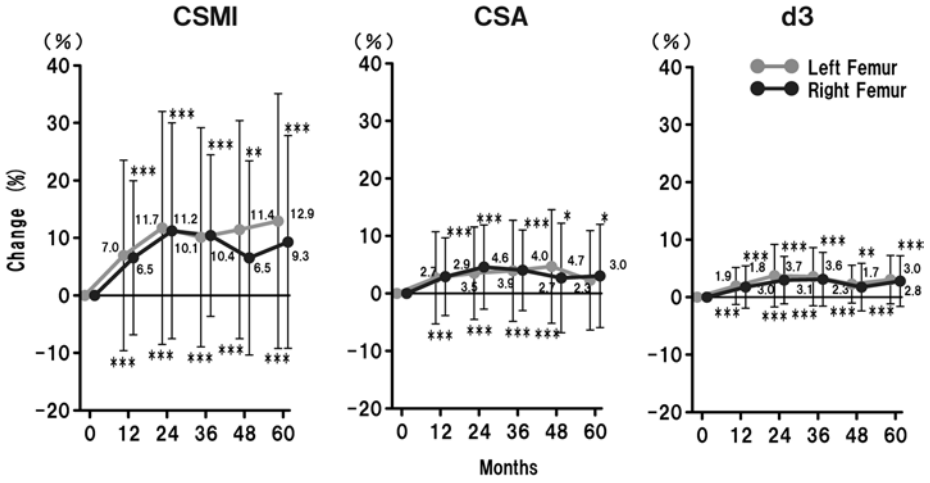

Fig. 4. Percent Changes in Advanced Hip Assessment (AHA) Parameters of the Femur

Data are expressed as mean±standard deviation. The paired *t*-test was used to compare parameters among time points.*$p<0.05$, **$p<0.01$, ***$p<0.001$ *versus* baseline.

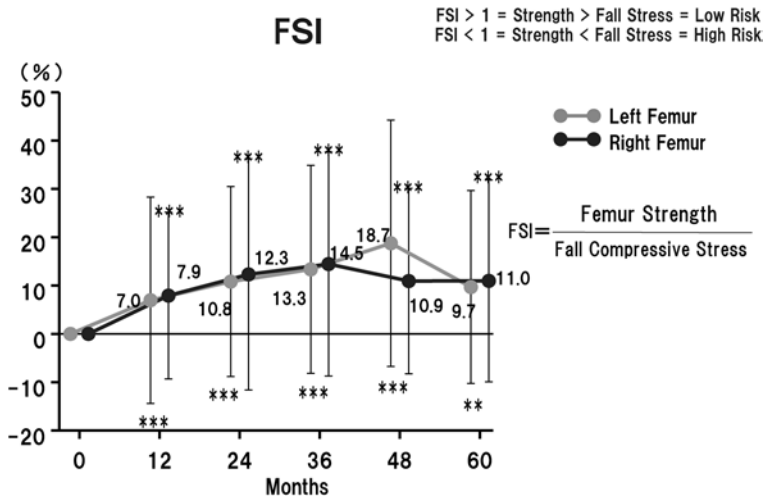

Fig. 5. Changes in the Femur Strength Index (FSI) during the Treatment

Data are expressed as mean±standard deviation. The paired *t*-test was used to compare the data at each time point with the baseline data. **$p<0.01$, ***$p<0.001$.

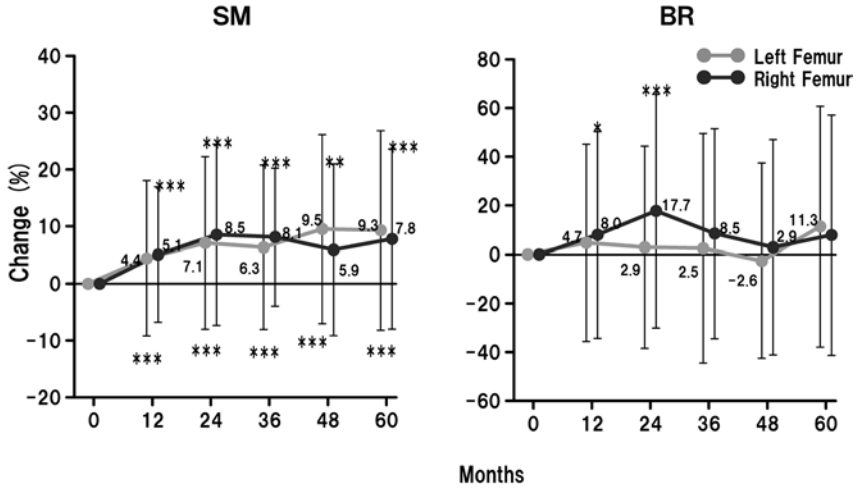

Fig. 6. Changes in Section Modulus (SM) and Buckling Ratio (BR) of the Femur during the Treatment

Data are expressed as mean±standard deviation. The paired *t*-test was used to compare the data at each time point with the baseline data. *$p<0.05$, **$p<0.01$, ***$p<0.001$.

evaluated the 1-year effect of once-weekly dosing with 17.5 mg of risedronate and once-daily dosing with 2.5 mg of risedronate under calcium supplementation (200 mg/d) on the lumbar spine BMD in Japanese patients with involutional osteoporosis.[18] Both risedronate dosing regimens similarly increased the lumbar spine BMD (5.36, 5.87%, respectively).[18] In the

present study, the lumbar spine BMD increased by 4.1% after 1-year of risedronate treatment, which was a smaller increase than that reported in the above-mentioned phase III study. One possibility for this discrepancy may be that neither calcium nor vitamin D was supplemented in our study. At least, vitamin D supplementation is considered to be important to obtain an adequate effect of bisphosphonates on BMD.[19,20]

Differences exist among bisphosphonates, including differences in the skeletal retention of the drug, speed of onset of effect, degree of bone turnover suppression, uptake in trabecular *versus* cortical bone (effects on osteocyte function and survival), anti-fracture effects, safety, and tolerability. Risedronate reduces the risk of clinical vertebral and nonvertebral fractures in patients with postmenopausal osteoporosis within 6 months of commencing treatment.[21,22] Based on our findings, it is reasonable to consider that the acute fracture prevention effect of risedronate is attributable to the ability of the drug to quickly increase the BMD and geometric parameters the BMD (most evident during the first 2 years). Additionally, the long-term fracture preventive effect of risedronate is attributable to further increases in or maintenance of these early effects. However, a different treatment strategy may be more appropriate for patients whose BMD continues to decline. Such a strategy may include switching to a different type of drug; *e.g.*, an anabolic agent such as parathyroid hormone, denosumab, or combination therapy with such drugs.[23–25] In particular, teriparatide and denosumab may be useful for increasing BMD in patients with postmenopausal osteoporosis.[25] However, in patients who showed the adequate response to risedronate treatment in terms of the greater increase in BMD beyond osteoporosis threshold, discontinuation of risedronate treatment together with vitamin D and calcium supplementation may be acceptable after 5 years of risedronate treatment.

Introduction of AHA to DXA permits calculation of the bone geometric parameters from a DXA scan, and a very high correlation has been confirmed between the femoral CMSI and CSA data obtained by DXA with AHA and those obtained by QCT.[4,5] Our study further confirmed the validity of this method and its clinical usefulness in evaluating the effect of risedronate, particularly its long-term effect on BMD, as well as the bone geometry and quality.

Despite the positive effects of risedronate on the femoral geometric parameters (CSMI, CSA, d3) and the FSI and SM of the femur, the BR of the femur poorly responded to risedronate treatment. The BR is an index of cortical stability under compressive loads and is calculated as the maximum distance from the centroid to the medial or lateral cortical margin divided by the estimated mean cortical thickness. These parameters are derived from a circular or elliptical annulus model of the cortex with a fixed fraction of measured mass in the cortex. Theoretically, risedronate suppresses endocortical bone resorption and thereby increases cortical thickness, resulting in an increase in the BR at the femoral neck cortex. However, d3 increased in our study, which might have been attributed to the increase in the BR. Takada *et al.*[26] also showed that risedronate treatment increased the outer diameter of the narrow neck of the femur in postmenopausal women with osteoporosis, although the increase was quite modest (0.25% after 1 year of treatment). The increase in d3 in our study is speculated to have resulted from an increase in the mineralization of cortical bone, which the DXA machine was able to detect with the cortical bone at the periosteal site. However, further studies are needed to clarify the influence of risedronate on cortical bone.

Among anti-osteoporosis medicines, alendronate, risedronate, zoledronic acid, and denosumab are confirmed to have the efficacy against vertebral, nonvertebral, and hip fractures in patients with postmenopausal osteoporosis.[27] Zoledronic acid is not available in Japan, and denosumab was not approved in the beginning of the present study. Therefore, alendronate or risedronate was the first line medicine in the treatment of osteoporosis. How long patients with osteoporosis should continue risedronate treatment is debatable. Compston and Bilezikian[28] suggest that the benefits and risks of both continuation and discontinuation must be considered in deciding the optimal duration of treatment. Long-term treatment is associated with fracture reduction but may increase the risk of rare adverse effects such as ONJ and atypical fractures, whereas discontinuation might reduce the risk of ONJ and atypical fractures but may also be associated with reduced protection against fractures.[28] Nevertheless, the strength of evidence for fracture reduction in high-risk patients and the rarity of long-term adverse effects indicate that in the majority of individuals, the benefits of continued treatment outweigh the risks and suggest that treatment should be continued on a long-term basis in individuals who continue to have a high risk of fracture.[28] Mellströmet *et al.*[29] reported that 7 years of continuous risedronate treatment increased BMD, decreased bone turnover to within premenopausal levels, and sustained anti-fracture efficacy in patients with postmenopausal osteoporosis, suggesting the long-term efficacy of risedronate treatment. In the present study, no serious adverse events, including ONJ or atypical femoral fractures,[16,17] were observed in patients treated with risedronate for 5 years.

A limitation of this study is the lack of a control group; this may have resulted in bias in the observed effects of risedronate. However, a steady increase in the vertebral BMD and significant increases in the femoral FSI, CSMI, CSA, d3, and SM from baseline during the 5-year treatment were demonstrated. Because these observations are consistent with most previous studies,[6–10] we believe that our results are clinically valid. It should be noted that the DXA images were obtained from the mineral distribution pattern and that the geometric parameters calculated from the DXA images may not necessarily reflect the true geometry. This is particularly true for calculated data such as the BR, which can only be crudely estimated from the DXA data.[15] QCT should be superior in this regard. Indeed, recent studies have demonstrated that reductions in the QCT-assessed BR are well correlated with improvements in the CSMI, CSA, and BMD.[30,31] Despite these limitations, our study has clearly demonstrated the long-term therapeutic efficacy of risedronate. DXA with AHA may ensure easy and accurate measurement of the BMD and bone geometry in terms of bone quality in clinical practice, both of which reflect bone strength.

In conclusion, DXA with AHA provided evidence that risedronate given at 2.5 mg/d or 17.5 mg/week for 5 years effectively increases the vertebral BMD and maintains the BMD of the femoral neck and total hip in patients with osteoporosis or osteopenia and clinical risk factors for fractures. Risedronate also improves the geometric parameters of the femur, includ-

ing the FSI, CSMI, CSA, d3, and SM, indicating the fracture-preventing effect of this therapy.

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Conflict of Interest No funding was received for this study. Yoshinori Suzuki is the product manager of Eisai Co., Ltd., Tokyo, Japan, who dealt with the risedronate. The other authors have no conflict of interest that is directly relevant to the content of this study.

REFERENCES

1) NIH Consensus Development Panel. Osteoporosis prevention, diagnosis, and therapy. *JAMA*, **285**, 785–795 (2001).
2) Yoshikawa T, Turner CH, Peacock M, Slemenda CW, Weaver CM, Teegarden E, Markwardt P, Burr DB. Geometric structure of the femoral neck measured using dual-energy X-ray absorptiometry. *J. Bone Miner. Res.*, **9**, 1053–1064 (1994).
3) Faulkner KG, Wacker WK, Barden HS, Simonelli C, Burke PK, Ragi S, Del Rio L. Femur strength index predicts hip fracture independent of bone density and hip axis strength. *Osteoporos. Int.*, **17**, 593–599 (2006).
4) Ramamurthi K, Ahmad O, Engelke K, Taylor RH, Zhu K, Gustafsson S, Prince RL, Wilson KE. An *in vivo* comparison of hip fracture analysis (HSA) with measurements obtained by QCT. *Osteoporos. Int.*, **23**, 543–551 (2012).
5) Ohnaru K, Sone T, Tanaka K, Akagi K, Ju Y-I, Choi H-J, Tomomitsu T, Fukunaga M. Hip structure analysis: a comparison of DXA with CT in postmenopausal Japanese women. *Springer Plus*, **2**, 331 (2013).
6) Reginster J-Y, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, Lund B, Ethgen D, Pack S, Roumagnac I, Eastell R. Randomized trial of the effects of risedronate on vertebral fractures I women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *Osteoporos. Int.*, **11**, 83–91 (2000).
7) Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, Chesnut CH 3rd, Brown J, Eriksen EF, Hoseyni MS, Axelrod DW, Miller PD. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *JAMA*, **282**, 1344–1352 (1999).
8) McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, Adami S, Fogelman I, Diamond T, Eastell R, Meunier PJ, Wasnich RD, Greenwald M, Kaufman J-M, Chesnut CH, Reginster J-Y, Hip Intervention Program Study Group. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N. Engl. J. Med.*, **344**, 333–340 (2001).
9) Wells G, Granney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. *Cochrane Database Syst. Rev.*, **23**, CD004523 (2008).
10) Zhong ZM, Chen JT. Anti-fracture efficacy of risedronic acid in men: a meta-analysis of randomized controlled trials. *Clin. Drug Investig.*, **29**, 349–357 (2009).
11) Takakuwa M, Iwamoto J, Konishi M, Zhou Q, Itabashi K. Risedronate improves proximal femur bone density and geometry in patients with osteoporosis or osteopenia and clinical risk factors of fractures: a practice-based observational study. *J. Bone Miner. Metab.*, **29**, 88–95 (2011).
12) Takakuwa M, Iwamoto J, Itabashi K. Three-year experience with risedronate therapy for patients with an increased fracture risk. Assessment of femoral bone density and geometry by DXA. *Clin. Drug Investig.*, **32**, 121–129 (2012).
13) Orimo H, Sugioka Y, Fukunaga M, Muto Y, Hotokebuchi T, Gorai I, Nakamura T, Kushida K, Tanaka H, Ikai T, Oh-hashi Y. Diagnostic criteria of primary osteoporosis. *J. Bone Miner. Metab.*, **16**, 139–150 (1998).
14) Orimo H, Hayashi Y, Fukunaga M, Sone T, Fujiwara S, Shiraki M, Kushida K, Miyamoto S, Soen S, Nishimura J, Oh-hashi Y, Hosoi T, Gorai I, Tanaka H, Igai T, Kishimoto H. Osteoporosis Diagnostic Criteria Review Committee, Japanese Society for Bone Mineral Research. Diagnostic criteria for primary osteoporosis: year 2000 revision. *J. Bone Miner. Metab.*, **19**, 331–337 (2001).
15) Beck TJ, Petit MA, Wu G, LeBoff MS, Cauley JA, Chen Z. Does obesity really make femur stronger? BMD, geometry, and fracture incidence in the Women's Health Initiative-Observational Study. *J. Bone Miner. Res.*, **24**, 1369–1379 (2009).
16) Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, Gagel RF, Gilsanz V, Guise T, Koka S, McCauley LK, McGowan J, McKee MD, Mohla S, Pendrys DG, Raisz LG, Ruggiero SL, Shafer DM, Shum L, Silverman SL, Van Poznak CH, Watts N, Woo SB, Shane E. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J. Bone Miner. Res.*, **22**, 1479–1491 (2007).
17) Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung AM, Cosman F, Curtis JR, Dell R, Dempster DW, Ebeling RR, Einhorn TA, Genant HK, Geusens P, Klaushofer K, Lane JM, McKiernan F, McKinney R, Ng A, Nieves J, O'Keefe R, Papapoulos S, Howe TS, van der Meulen MC, Weinstein RS, Whyte MP. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. *J. Bone Miner. Res.*, **29**, 1–23 (2014).
18) Kishimoto H, Fukunaga M, Kushida K, Shiraki M, Itabashi A, Nawata H, Nakamura T, Ohta H, Takaoka K, Ohashi Y; Risedronate Phase III Research Group. 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 (2006).
19) Ishijima M, Sakamoto Y, Yamanaka M, Tokita A, Kitahara K, Kaneko H, Kurosawa H. Minimum required vitamin D level for optimal increase in bone mineral density with alendronate treatment in osteoporotic women. *Calcif. Tissue Int.*, **85**, 398–404 (2009).
20) Ringe JD, Farahmand P, Schacht E, Rozehnal A. Superiority of a combined treatment of Alendronate and Alfacalcidol compared to the combination of Alendronate and plain vitamin D or Alfacalcidol alone in established postmenopausal or male osteoporosis (AAC-Trial). *Rheumatol. Int.*, **27**, 425–434 (2007).
21) Roux C, Seeman E, Eastell R, Adachi J, Jackson RD, Felsenberg D, Songcharoen S, Rizzoli R, Di Munno O, Horlait S, Valent D, Watts NB. Efficacy of risedronate on clinical vertebral fractures within six months. *Curr. Med. Res. Opin.*, **20**, 433–439 (2004).
22) Harrington JT, Ste-Marie LG, Brandi ML, Civitelli R, Fardellone P, Grauer A, Barton I, Boonen S. Risedronate rapidly reduces the risk for nonvertebral fractures in women with postmenopausal osteoporosis. *Calcif. Tissue Int.*, **74**, 129–135 (2004).
23) Kawai M, Mödder UI, Khosla S, Rosen CJ. Emerging therapeutic opportunities for skeletal restoration. *Nat. Rev. Drug Discov.*, **10**, 141–156 (2011).
24) Das S, Crockett JC. Osteoporosis—a current view of pharmacological prevention and treatment. *Drug Des. Devel. Ther.*, **7**, 435–448 (2013).
25) Cummings SR, Cosman F, Eastell R, Reid IR, Mehta M, Lewiecki EM. Goal-directed treatment of osteoporosis. *J. Bone Miner. Res.*, **28**, 433–438 (2013).

26) Takada J, Katahira G, Iba K, Yoshizaki T, Yamashita T. Hip structure analysis of bisphosphonate-treated Japanese postmenopausal women with osteoporosis. *J. Bone Miner. Metab.*, **29**, 458–465 (2011).
27) Murad MH, Drake MT, Mullan RJ, Mauck KF, Stuart LM, Lane MA, Abu Elnour NO, Erwin PJ, Hazem A, Puhan MA, Li T, Montori VM. Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis. *J. Clin. Endocrinol. Metab.*, **97**, 1871–1880 (2012).
28) Compston JE, Bilezikian JP. Bisphosphonate therapy for osteoporosis: the long and short of it. *J. Bone Miner. Res.*, **27**, 240–242 (2012).
29) Mellström DD, Sörensen OH, Goemaere S, Roux C, Johnson TD, Chines AA. Seven years of treatment with risedronate in women with postmenopausal osteoporosis. *Calcif. Tissue Int.*, **75**, 462–468 (2004).
30) Anitha D, Kim KJ, Lim SK, Lee T. Implications of local osteoporosis on the efficacy of anti-resorptive drug treatment: a 3-year follow-up finite element study in risedronate-treated women. *Osteoporos. Int.*, **24**, 3043–3051 (2013).
31) Ito M, Oishi R, Fukunaga M, Sone T, Sugimoto T, Shiraki M, Nishizawa Y, Nakamura T. The effects of once-weekly teriparatide on hip structure and biomechanical properties assessed by CT. *Osteoporos. Int.*, **25**, 1163–1172 (2014).