score showed negative correlation with age ($r = -0.183$). The subjects with vertebral fractures had significantly lower JOQOL scores than the subjects without fractures. The JOQOL showed a significant correlation with all the scores in each domain of eight of SF-36 ($r = 0.350$–0.839). These results were consistent with that of the preceding study. It is concluded that the reliability and the validity of JOQOL were demonstrated in this study.

Keywords Reliability · Validity · Health-related QOL · Vertebral fracture · Osteoporosis

Introduction

Osteoporosis is a common metabolic bone disease that weakens bone strength, aggravates bone fragility, and increases susceptibility to fracture [1, 2]. The prevalence of osteoporosis increases with aging; in particular, it increases sharply in women around age 45 in the menopausal period. For women in their late seventies, the prevalence exceeds 50% [3]. Vertebral fracture risk is high in patients with osteoporosis. A vertebral fracture brings about many disabilities such as a change in posture (kyphosis), decline in physical functioning, and persistent back pain. These symptoms of the vertebral fracture decrease the quality of life (QOL) of the patient [4]. Thus, in the treatment of the osteoporosis, the consideration of patients' QOL is important [5, 6].

Quality of life has been defined by the World Health Organization (WHO) [7] as "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". QOL is roughly divided into two types, such as QOL having a direct connection with health (health-related QOL, HRQOL), and QOL not having a direct connection with health. The HRQOL is a QOL that influences the health of the person directly in terms of physical state, psychosocial state, role function, and well-being. There are two types in the HRQOL, the general HRQOL and disease-specific HRQOL. General HRQOL are generic measures that are broadly applicable and can be used across patient populations. Medical Outcomes Study Short Form 36 (SF-36) [8] is the most widely evaluated measure [9]. EQ-5D (EuroQOL) [10] and the sickness impact profile (SIP) [11] have been also widely used as general HRQOL measurements. Disease-specific HRQOL is focused on aspects of health problems caused by specific disease or impairment. There are many measures that are specific to certain health problems. As disease-specific HRQOL measurements for osteoporosis, Qualeffo [12, 13], OPAQ [14], OQLQ [15, 16], and OPTQoL [17] have been developed in Western countries.

The Japanese Society for Bone and Mineral Research composed the Japanese Osteoporosis Quality of Life Questionnaire (JOQOL) to evaluate the disease-specific HRQOL for osteoporosis that is specific to Japanese patients. JOQOL was completed in 2000 [18]. Although many studies have been conducted to evaluate the disease-specific HRQOL of osteoporosis patients with JOQOL [19–23], the reliability and validity of the JOQOL have not been fully confirmed yet. Therefore, the aim of this study was to elucidate the reliability and validity of the JOQOL.

Subjects and methods

Subjects

We enrolled 195 postmenopausal women who had been diagnosed with osteoporosis or osteopenia from January to December 2005. They were recruited from outpatient departments of four hospitals as follows: Obstetrics and Gynecology Department of Atami Hospital of International University of Health and Welfare; Research Institute and Practice for Involutional Diseases; Orthopedic Surgery Department of Medical and Dental Hospital of Niigata University; and Department of Gynecology of Tokyo Women's Medical University.

Because of the exclusion of 2 patients with obvious disabilities (motor paralysis) resulting from a cerebrovascular incident, 193 patients were analyzed in this study.

The study on the test–retest reliability of the JOQOL required repetitive survey with questionnaires and patients' stable conditions. We set the interval from more than 2 to 5 weeks between the test and retest. Among 193 patients, 83 from two hospitals (Obstetrics and Gynecology Department of Atami Hospital of International University of Health and Welfare and Orthopedic Surgery Department of Medical and Dental Hospital of Niigata University) participated in the study to confirm the retest reliability. No patient had experienced a bone fracture or an operation between the period from test to retest. The mean lapse from the test to retest was 23.7 (SD 9.5) days.

Diagnosis

In this study, the diagnosis criteria of osteoporosis or osteopenia were according to the diagnostic criteria for osteoporosis that were established by the Japanese Society for Bone and Mineral Research. These criteria provided that bone mineral density (BMD) <80% of the young adult mean was osteopenia and that <70% was osteoporosis [24].

An orthopedist in charge of the patient diagnosed osteopenia/osteoporosis by BMD of two to four lumbar vertebrae. BMD was measured by dual-energy X-ray absorptiometry (DXA) within 6 months before the start of the survey. The four hospitals used different types of DXA (DPX series from Lunar, QDR series from Hologic, and XR series from Norland), and consequently the criteria were applied to the subjects at each hospital.

Methods

Measures

Development of JOQOL

The development of JOQOL was consistent with widely accepted strategies for scale development.

First, a committee that consisted of orthopedists, internists, gynecologist, epidemiologist, and physiotherapist reviewed the measurements of the disease-specific HRQOL of osteoporosis patients currently used in Western countries. The committee generated a list of items, which was based on the Osteoporosis Assessment Questionnaire (OPAQ) with a version of 79 items, by Silverman et al. [14] and the Qualeffo-41 by Lips et al. [12, 13], both Japanese versions made with the author's permission, and some items particular to the Japanese lifestyle were added.

Second, those items were reduced to 40 items as a result of statistical examination of the reliability and the validity in field-testing [25, 26].

Third, the reliability and validity of the JOQOL (40 items version) were assessed as follows. The subjects were 198 patients of osteoporosis (mean age 70.5 years; SD 9.5 years). Cronbach's alpha, which was the internal consistency of a total score, was 0.808. Test–retest reliability of the JOQOL was assessed in 83 patients 4 weeks apart, and the correlation coefficient was 0.920. There was a significant difference of the score between those with a compression fracture of the vertebrae and those without fracture ($p < 0.001$) [27]. The 40 items version of JOQOL showed generally a good result, but it was recognized that some items were inappropriate as a measurement. Then, the committee revised JOQOL from the study data [28].

The latest JOQOL consists of 38 items with the scale graded from 0 to 4 and a total full score of 152. The total score is converted into percentage; patients' HRQOL is regarded as higher with the higher score. Although 38 items were sorted into six domains according to the contents of questions, the committee recommends use in the total score [18] (see Electronic Supplementary Material). After the revision, reliability and validity of the JOQOL have not been confirmed.

Instrument testing

The reliability of JOQOL was examined in terms of test–retest reliability and internal consistency. The test–retest reliability is the stability of the evaluation with time, and the agreement of the results from two times of evaluation is examined. Internal consistency measures whether the items are those intended to measure the same construct. It is usually measured with Cronbach's alpha, which is a measure based on the correlations between different items on the same test or the same subscale.

To inspect the consistent validity of JOQOL, we examined whether the previous findings about the other disease-specific HRQOLs for the osteoporotic patients were also shown in JOQOL. It is known that the disease-specific HRQOL for the osteoporosis patient is related to whether they have a vertebral fracture, and this deteriorates with age [6, 29, 30]. In addition, to examine the concurrent validity of JOQOL, we estimated the relationship between JOQOL and a general HRQOL. In this study, we selected SF-36 as the general HRQOL. The SF-36 is a widely used general HRQOL measurement with 36 questions. It consists of an 8-scale profile of functional health and well-being scores.

Each patient was asked to complete a self-report questionnaire, which consisted of (1) JOQOL, (2) SF-36, (3) questions on their characteristics, and (4) questions on their performance of activities of daily living (ADL). We obtained the patients' written informed consent and handed them the questionnaire. Then, the questionnaire was completed by them at home and returned by mail. An omission of any answer of the questionnaire was confirmed over the telephone or at the time of outpatient consultation.

The incidence of vertebral fractures was also examined. The number of the vertebral fractures was counted by orthopedists with the thoracic and lumbar vertebrae (T3–L5) X-ray taken in two directions (anteroposterior and lateral). In counting fractures, we used X-ray photographs taken within 3 months before the start of the survey. If a patient had a suspicious incidence of vertebral fracture within 3 months before the start, we obtained a new X-ray photograph.

Statistical analysis

The test–retest reliability of the total score of JOQOL was examined by Pearson's product moment correlation coefficient and paired t test. As a reliability coefficient of each JOQOL item, Kendall's τ (b) rank correlation coefficient was calculated. The internal consistency was examined by a Cronbach's alpha coefficient.

The consistent validity of the JOQOL was examined with t test by comparison of having vertebra fracture or not

of the patients. The concurrent validity of JOQOL, we estimated the Pearson's correlation coefficient between JOQOL and SF-36.

Statistical significance was set at $p < 0.05$ and SPSS (version 12.0 J) was used for the foregoing statistical analyses.

Results

The mean age of the entire group of study subjects was 68.2 (SD 8.0) years, ranging from 48 to 86 years. Their mean height was 150.5 (SD 5.7) cm; mean weight was 50.4 (SD 6.6) kg; mean body mass index (BMI) was 21.8 (SD 3.0) kg/m^2; and mean BMD was 0.759 (SD 0.173) g/cm^2. Among the samples of this study, 58 patients (30.1%) had at least one vertebral fracture and 44 (22.8%) had one to three fractures (Table 1). There was no subject with ADL deficit. Table 2 shows the characteristics of the subjects with or without vertebral fractures. Statistically significant differences were found for age. Table 3 shows the results of the JOQOL and SF-36. The mean score of JOQOL was 71.9 (SD 12.6).

Table 1 Numbers of vertebral fractures

Number	Case	Percent (%)
0	135	69.9
1	18	9.3
2	10	5.2
3	16	8.3
4	2	1.0
5	2	1.0
6	6	3.1
7	1	0.5
8	1	0.5
10	2	1.0
Total	193	100.0

Reliability

The test and retest scores of JOQOL were significantly correlated ($r = 0.973$, Fig. 1). The first and second mean scores of JOQOL were 67.8 (SD 15.3) and 67.7 (SD 15.5), respectively, and no significant difference was observed between them.

We calculated the Kendall's τ for each JOQOL item (Table 4), and all items showed significant correlations at the time of test and retest ($\tau = 0.599$–0.947). The Cronbach's alpha coefficient of JOQOL was 0.918.

Validity

The Pearson's correlation coefficients among scores of JOQOL, patient's age, and BMI were $r = -0.183$, 0.058, respectively. The JOQOL score was significantly correlated with the age of patients. Table 5 shows a comparison of JOQOL and SF-36 scores between a group of patients who had one or more vertebral fractures ($n = 58$) and that of patients without vertebral fracture ($n = 135$). There was a significant difference between these two groups in the JOQOL scores, whereas significant difference was found only in two domains (Physical Functioning and Role Physical) among eight domains of SF-36. As shown in Table 6, scores in each domain of eight of the SF-36 were significantly correlated to the JOQOL score ($r = 0.350$–0.839).

Discussion

Japanese Osteoporosis Quality of Life Questionnaire was already used widely as the disease-specific HRQOL measurement for osteoporosis patients in Japan; therefore, it has been accepted that JOQOL has adequate content validity, among experts. Although the validation of the JOQOL before the minor revision had been confirmed, the validation of the latest JOQOL has not been carried out yet. Therefore, we conducted this study to confirm its reliability and validity.

The JOQOL scores at the time of test and retest showed a high correlation with the mean lapse of 24 days, and this

Table 2 Characteristics of subjects with and without vertebral fractures

	Without vertebral fracture ($n = 135$)		With vertebral fracture ($n = 57$)		p value (t test)
	Mean	SD	Mean	SD	
Age (years)	66.7	7.4	71.8	8.4	0.000
Height (cm)	151.0	5.6	149.3	5.3	0.065
Body weight (kg)	49.0	6.5	49.0	8.0	0.993
BMI (kg/m^2)	21.6	2.9	22.2	3.2	0.256

BMI Body mass index

Table 3 Mean scores of Japanese Osteoporosis Quality of Life Questionnaire (JOQOL) and SF-36

	Mean	SD
JOQOL	71.9	12.6
SF-36 physical function	76.6	23.1
SF-36 role physical	65.5	32.5
SF-36 body pain	65.7	24.8
SF-36 general health	54.2	21.3
SF-36 vitality	56.3	22.3
SF-36 social functioning	80.8	24.1
SF-36 role emotion	69.6	32.7
SF-36 mental health	68.4	21.4

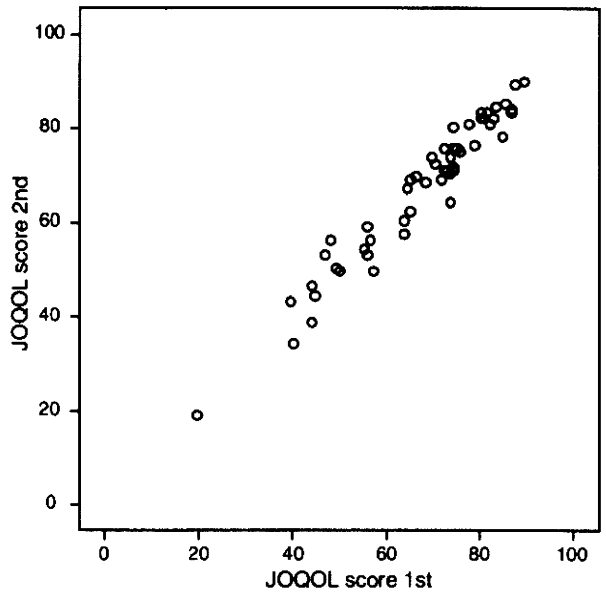

Fig. 1 Correlation between test and retest score of Japanese Osteoporosis Quality of Life Questionnaire (*JOQOL*). Pearson's correlation coefficient: $r = 0.973$, $p < 0.001$

finding indicated their high test–retest reliability. The Cronbach's alpha coefficient of JOQOL was 0.918, which showed high internal consistency. Thus, these results proved the high reliability of JOQOL.

Each of the 38 items that constitute JOQOL showed approximately 0.6 or higher rank correlation coefficients with time lapse, indicating sufficient test–retest reliability of each item of JOQOL. This result suggests test–retest reliability of any measurements that consist of JOQOL items such as a subscale of JOQOL.

The previous studies reported that disease-specific HRQOL for the osteoporosis patient were worsened when there was a vertebral fracture, and there were a large number of vertebral fractures. In the present study, patients without a vertebral fracture comprised 70% of all the subjects. Thus, we divided the subjects into two groups according to the presence of vertebral fracture and compared their JOQOL scores. Then, a significant difference between the two groups was recognized, and the JOQOL score showed a negative correlation with age. These findings were consistent with the results of preceding studies [6, 29–31].

Table 4 The test–retest reliability of JOQOL items

Item	Kendall's τ	*p*
Q1	0.724	**
Q2	0.691	**
Q3	0.712	**
Q4	0.818	**
Q5	0.749	**
Q6	0.799	*
Q7	0.653	**
Q8	0.787	**
Q9	0.790	*
Q10	0.749	**
Q11	0.850	**
Q12	0.800	**
Q13	0.851	**
Q14	0.790	**
Q15	0.788	**
Q16	0.861	**
Q17	0.798	**
Q18	0.725	**
Q19	0.940	**
Q20	0.947	**
Q21	0.933	**
Q22	0.674	**
Q23	0.828	**
Q24	0.751	**
Q25	0.670	**
Q26	0.758	**
Q27	0.724	**
Q28	0.805	**
Q29	0.666	**
Q30	0.681	**
Q31	0.855	**
Q32	0.631	**
Q33	0.654	**
Q34	0.616	**
Q35	0.730	**
Q36	0.632	**
Q37	0.599	**
Q38	0.675	**

* $p < 0.05$, ** $p < 0.01$

Table 5 Comparison of JOQOL and SF-36 scores between patients with or without fractures

	With vertebral fracture		Without vertebral fracture		*p* value (*t* test)
	Mean	SD	Mean	SD	
JOQOL	66.7	15.6	74.2	10.3	0.01
SF-36 domains					
Physical function	66.1	29.0	81.2	18.3	0.00
Role physical	57.3	35.6	69.2	30.4	0.04
Body pain	61.3	27.3	67.6	23.5	0.15
General health	49.7	22.0	56.2	20.8	0.09
Vitality	53.2	22.5	57.7	22.2	0.26
Social functioning	79.0	25.0	81.7	23.8	0.53
Role emotional	65.1	34.7	71.6	31.7	0.27
Mental health	69.3	16.8	68.0	23.2	0.69

Table 6 Pearson's correlation coefficients between JOQOL and SF-36

SF-36 domain	JOQOL	*p*
Physical function	0.839	**
Role physical	0.463	**
Body pain	0.665	**
General health	0.562	**
Vitality	0.521	**
Social functioning	0.464	**
Role emotional	0.350	**
Mental health	0.483	**

** $p < 0.01$

To confirm the concurrent validity of the JOQOL, it is required to examine the relationship between JOQOL and the other HRQOL. We examined correlation with well-established general HRQOL; it has been a widely used method in this kind of study [6, 13, 29]. In previous studies, EQ-5D, a widely used general HRQOL measurement, showed significant correlation with JOQOL [22, 31]. In this study, SF-36, which is one of the most widely used general HRQOL, was selected. In the subjects, the scores in each domain of eight domains of SF-36 indicated significant correlation with JOQOL. Thus, these results proved the concurrent validity of the JOQOL.

In this study, we were not able to prove the disease specificity of JOQOL sufficiently because the subjects consisted of osteoporosis patients only and because of the omission of a control group and patients with physical impairment or other diseases. This limitation should be a future subject to be resolved.

In conclusion, the reliability and the validity of JOQOL were confirmed in this study. Therefore, JOQOL should be expected to be utilized further as a disease-specific HRQOL measurement for osteoporosis patients in Japan.

Acknowledgments We are grateful to the collaborating members of JSBMR: Kunihiko Aoyama, Junji Inoue, Kinichi Ueno, Sumiaki Okamoto, Takeshi Kiriyama, Toshiyuki Konno, Takenori Sakada, Saburo Nishida, Hiromichi Norimatsu, Teruo Haba, Satoshi Mori, Akira Itabashi, and Masao Fukunaga. We are also grateful to Kazuo Endo, Hiroe Ishigaki, Shinichi Fukuhara, Yoshimi Suzukamo, Erika Kobayashi, and Hajime Iwasa who collaborated in this study.

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J Bone Miner Metab (2010) 28:334–341
DOI 10.1007/s00774-009-0138-7

ORIGINAL ARTICLE

Effect of minodronic acid hydrate on hip geometry in Japanese women with postmenopausal osteoporosis

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Received: 9 July 2009 / Accepted: 8 October 2009 / Published online: 25 November 2009

Abstract Dual-energy X-ray absorptiometry-based hip structural analysis was performed to evaluate the effect of a bisphosphonate, minodronic acid hydrate, on the geometry of the proximal femur in Japanese patients with osteoporosis. The subjects were 103 postmenopausal patients (average age 63.9 ± 6.4 years) with primary osteoporosis. Minodronic acid hydrate was administered orally at a dose of 1 mg/day for 12 months. Significant early responses at 3–6 months after the start of administration were observed in all three regions of the proximal femur (narrow neck, intertrochanter, and shaft) in terms of bone density, geometry, and bone strength indices. The outcomes of therapy included a reduction of the internal diameter of the cortical bone (−0.1, −0.6, and −0.2% in the neck, intertrochanter, and shaft, respectively, at 12 months; not significant) and a significant increase in cortical thickness (3.1, 3.7, and 2.0% in the respective regions at 12 months). Furthermore, minodronic acid hydrate induced a significant enlargement of the cross-sectional bone area, which is related to compressive strength; a significant increase in cross-sectional moment of inertia and section modulus (SM 4.9, 5.8, and 2.9% in the neck, intertrochanter, and shaft, respectively, at 12 months; $P < 0.001$), which are related to the bending strength; and a significant reduction in buckling ratio (BR −3.0% ($P < 0.001$), −4.2% ($P < 0.001$), and −1.4% ($P < 0.05$) in the respective regions at 12 months), which reflects improved cortical stability. These findings show that minodronic acid hydrate reduces age-related endocortical bone resorption, leading to increased cortical thickness and sustained or enhanced bone strength.

Keywords Bisphosphonate · Minodronic acid hydrate · Hip geometry · Osteoporosis

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Introduction

Bone geometry refers to bone tissue distribution and alignment, which are critical for both the structural and biomechanical properties of bone [1]. For those parts of the skeletal system with a complex shape, such as the proximal femur, bone geometry plays a particularly important role in biomechanical assessment. In this context, the hip structure analysis (HSA) algorithm was developed for noninvasive clinical evaluation of dual X-ray absorptiometry (DXA) of the proximal femur [2]. Three prominent prospective epidemiological studies demonstrated the ability of this method to predict hip fracture using analysis of hip geometry. In a prospective case–control study of 71 women and 25 men more than 60 years old [3], the femoral neck diameter, cross-sectional moment of inertia (CSMI), and section modulus (SM) were identified as independent predictors of hip fracture risk after adjustment for bone mineral density (BMD) in both women and men. However, the contribution of these measures to hip fracture prediction over and above BMD is likely modest. A part of the Rotterdam study included 147 incident hip fracture cases in 4806 participants [4]; the geometrical parameters did not have a better discrimination than BMD, and the buckling ratio did not offer additional predictive value. Among 7474

women from the Study of Osteoporosis Fracture (SOF) with hip DXA at baseline, 635 incident hip fractures were recorded over 13 years [5]. HSA showed the geometrical parameters, and biomechanical parameters derived from them were not more able than BMD to predict hip fracture.

This limitation may be linked to the ex vivo measurement of the cross-sectional femoral neck geometry and bone density using high-resolution computed tomography (CT), which has shown that site-dependent cortical thickness and a shifted centroid are important geometrical parameters related to bone strength [6]. HSA based on the two-dimensional bone density distribution is limited to an evaluation of the morphology of the cross section of the femoral neck, including the local cortical thickness and centroid in the cross-sectional femoral neck. Moreover, the HSA program is also limited, because most of the derived geometrical parameters depend on assumptions regarding the cross-sectional shape and on fixed percentages of cortical bone, and all the parameters are derived from bone density.

The evaluation of hip fracture risk following drug intervention requires a different point of view from that taken in epidemiological studies. The purpose of a prospective epidemiological study is to identify risk factors (e.g., geometry, BMD) that have a significant association with a future fracture. In contrast, the purpose of an intervention study is to determine whether the assessment tool (i.e., HSA) can detect a change in bone geometry and density of an individual patient after treatment, and to show whether the intervention induces an enhancement of bone strength. Taking bone geometry and BMD into account may improve the accuracy of an assessment of bone strength because an antiosteoporotic drug may modify bone geometry as well as density. A treatment-induced increase in bone density that involves an overall change in bone mass, bone size, and bone mineralization also affects bone biomechanical properties. The DXA–BMD value is influenced by all these changes but does not afford a means to determine how much the medication may influence bone biomechanical properties, because an observation of elevation in bone mass/mineralization may be offset by an increase in bone size. Therefore, evaluation of changes in bone density and geometry based on simultaneous measurement of different indices is required to properly gauge the response to treatment.

Minodronic acid hydrate is a new third-generation bisphosphonate with potent pharmacological activity that has been developed in Japan. Nonclinical studies have shown that this agent is a strong inhibitor of bone resorption at low doses [7], with inhibitory effects on the reduction of bone density or strength that are comparable with those of other bisphosphonates [8, 9]. A clinical study showed that administration of minodronic acid hydrate at 1 mg/day for 12 months produced increases of 6.0% in average lumbar bone density (L2–L4) and 3.6% in total bone density of the proximal femur in Japanese postmenopausal female patients with osteoporosis [10]. This trial also provided the first evidence that minodronic acid hydrate was superior to a placebo in preventing vertebral body fracture, with 2-year cumulative incidence of vertebral body fracture of 10.4% in the treatment group and 24.0% in the placebo group, corresponding to a 59% reduction in the relative risk of vertebral body fracture over 2 years [11]. In the present study, we report the effects of minodronic acid hydrate on hip geometry in Japanese female patients with osteoporosis, the first report of HSA results in a multicenter clinical trial in Japan.

Materials and methods

Subjects

The subjects were 103 postmenopausal female ambulatory patients with osteoporosis (>45 years old; average age, 63.9 ± 6.4 years) who were enrolled at 43 centers. Osteoporosis was defined by the criteria of the Japanese Society for Bone and Mineral Research [12, 13]. The exclusion criteria have been given elsewhere [10]. The 103 patients were not selected deliberatory from the original clinical trial (n = 135). The other 32 hip DXA data cases were obtained by the previous version of the QDR4500 series, or the DXA data were not adapted for the HSA program. The characteristics of the subjects at baseline and 12 months after the start of administration are shown in Table 1, which shows the subjects in the present study were not a deliberately selected subgroup from the original clinical trial [10]. The subjects were asked to take a 1-mg minodronic acid hydrate tablet once daily for 12 months and to remain in an upright position for 30 min before the first food or beverage of the day after taking the medication. In addition to the study medication, all subjects received a 1.6-g oral dose of calcium lactate (200 mg elemental Ca) once a day after the evening meal. Vitamin D was not supplied as a supplement.

The study was conducted with consideration for the protection of subjects as outlined in the Declaration of Helsinki, and was approved by the appropriate institutional review boards. All subjects gave written informed consent before undergoing examinations or study procedures, which were conducted in compliance with Good Clinical Practice.

Methods

The BMD of the proximal femur was measured by DXA at baseline and 3, 6, 9, and 12 months after administration.

Table 1 Characteristics of subjects at baseline and after the administration of minodronic acid hydrate for 12 months

	Baseline	12 months	*P* value
Age (years)	63.9 ± 6.4	–	–
Body weight (kg)	50.0 ± 6.5	–	–
Body height (cm)	152.3 ± 4.7	–	–
Age at menopause (years)	49.9 ± 3.3	–	–
Lumbar spine BMD (g/cm^2)	0.648 ± 0.051	0.688 ± 0.060	<0.001
Total hip BMD (g/cm^2)	0.635 ± 0.078	0.657 ± 0.077	<0.001
Conventional neck BMD (g/cm^2)	0.542 ± 0.072	0.555 ± 0.070	<0.001
HSA			
Hip axis length (mm)	99.9 ± 5.2	–	–
Neck shaft angle (°)	125.6 ± 5.1	–	–
Bone biomarker			
Urine NTX (nmol BCE/mmol Cr)	53.2 ± 18.6	19.8 ± 9.7	<0.001
Urine total DPD (pmol/mmol Cr)	9.3 ± 2.8	4.5 ± 1.4	<0.001
Serum BALP (U/l)	30.1 ± 10.0	14.6 ± 4.3	<0.001
Serum osteocalcin (ng/ml)	9.3 ± 2.7	4.2 ± 1.0	<0.001

Each value is shown as the mean ± SD

BMD bone mineral density, *HSA* hip structure analysis, *NTX* urine type I collagen N-telopeptide, *DPD* urine total deoxypyridinoline, *BALP* serum bone-specific alkaline phosphatase

All DXA devices were of the Hologic QDR Series, and each machine was adjusted for differences by calibration with standard phantoms to verify the reproducibility of the measurements within ±1.5% during the study period. DXA image data for the proximal femur were analyzed using the HSA program (Version 12.7.3.1), and all analyses were conducted by the same technician (T.T.) in the Department of Nuclear Medicine, Kawasaki Medical School.

The HSA algorithm is based on a principle first articulated by Martin and Burr [14], who demonstrated that mineral profiles created during a single photon absorptiometry bone density scan are a projection of the corresponding bone cross section and can be used to define its geometry. As described previously [2, 15, 16], the HSA algorithm derives the conventional BMD (g/cm^2), the outer diameter (OD, cm), the endocortical diameter (ED, cm), the average cortical thickness (CoTh, cm), the total mineralized bone area in the cross section (CSA, cm^2), the cross-sectional moment of inertia (CSMI, cm^4), and the section modulus (SM, cm^3) directly from the mass profiles. SM is computed as CSMI/d_{max}, where d_{max} (cm) is the maximum distance between the center of the mass (centroid) and the outer cortex. Another parameter, the buckling ratio (BR), is estimated as the ratio of d_{max} to the estimated average CoTh derived from an annulus model of the cross section using the measured OD, assuming that a fixed proportion of CSA is in the cortex. CSA and SM are indices of resistance to axial compressive and bending loads, respectively, and BR is an index of susceptibility to local buckling under bending loads.

The HSA software generates profiles of pixel values traversing the proximal femur at three locations: the narrow neck (NN) across the femoral neck at its narrowest point, the intertrochanter (IT) along the angle bisector defined by the neck and shaft axes, and across the shaft at 30 mm below the most prominent portion of the lesser trochanter. To avoid variation in the visualization of the lower border of the lesser trochanter depending on the inner rotation of the hip joint, the distance from the highest part of the lesser trochanter was made constant to improve the reproducibility of bone shaft regions and to correctly determine the region of interest (ROI). At each of these locations, five parallel profiles were generated, spaced one pixel apart, proximal and distal to the three defined locations. The five profiles were averaged within each region, and the BMD, CSA, OD, ED, CoTh, CSMI, SM, and BR were reported. The reproducibility of the HSA parameters was calculated using two measurements at a 1- or 2-month interval from 30 women [age 56–86 years old (range 71.8 ± 7.6 years)] (Table 2).

Table 2 Reproducibility of HSA parameters in the three regions

	CV (%)		
	Neck	Trochanter	Shaft
Cross-sectional area	1.91	2.88	1.72
Subperiosteal width	2.15	1.40	0.65
Endocortical width	2.47	1.53	1.63
Cortical thickness	3.87	3.11	2.31
CSMI	6.10	4.80	2.17
Section modulus	3.50	4.11	1.81
Buckling ratio	5.54	3.11	2.74

The reproducibility was calculated using two measurements at 1- or 2-month intervals from 30 women

CV coefficient of variation, *HSA* hip structure analysis, *CSMI* cross-sectional moment of inertia

Statistical analysis

For each case, the change (%) from baseline was calculated for each parameter, and summary statistics were obtained at individual time points. These data are expressed as average values and standard deviations (SD). Comparison of the findings before and after administration of minodronic acid hydrate was performed by Wilcoxon test, assuming a two-sided level of significance of 5% ($P < 0.05$).

Results

Changes in BMD from baseline

Percentage changes in BMD of individual femoral regions from baseline are shown in Fig. 1. The BMD significantly increased in all regions after 3–6 months administration of minodronic acid hydrate and increased by 3.2% ($P < 0.001$), 4.1% ($P < 0.001$), and 1.6% ($P < 0.001$) in the NN, IT, and shaft, respectively, after 12 months. The largest change was observed in the trochanteric region. The femoral BMD, geometry, and bone strength indices at baseline and 12 months are shown in Table 3.

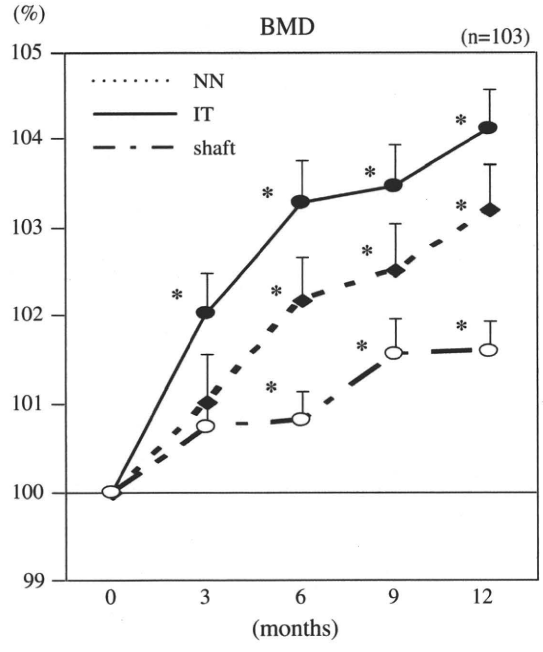

Fig. 1 Percentage changes from baseline of bone mineral density (*BMD*) in the femoral neck, trochanter, and shaft at 3, 6, 9, and 12 months of treatment. Data are shown as means ± SE ($n = 103$); *$P < 0.05$ versus baseline (Wilcoxon test). *NN* narrow neck, *IT* intertrochanter

Changes in bone geometry from baseline

Percentage changes in bone geometry from baseline are shown in Fig. 2. CSA significantly increased in all the femoral regions starting 3 months after administration and increased by 3.3% ($P < 0.001$), 3.9% ($P < 0.001$), and 2.0% ($P < 0.001$) in the NN, IT, and shaft after 12 months. The changes in OD from baseline were 0.1, −0.2, and 0.4% in the NN, IT, and shaft, respectively, at 12 months after administration, with none of these changes reaching a significant level, except for OD in the shaft at 12 months ($P = 0.015$). ED deceased from baseline by −0.1, −0.6, and −0.2% in the NN, IT, and shaft, respectively, after 12 months, showing a trend for a decrease but without significance in any region. CoTh significantly increased from baseline at 3 months after administration and increased by 3.1% ($P < 0.001$), 3.7% ($P < 0.001$), and 2.0% ($P < 0.001$) in the NN, IT, and shaft, respectively, after 12 months. Overall, the most significant changes were observed in IT.

Changes in bone strength indices from baseline

Percentage changes from baseline in CSMI, SM, and BR, all of which are bone strength indices for the femoral region, are shown in Fig. 3. CSMI and SM showed significant increases in all the femoral regions examined 3 months after administration; CSMI increased by 4.8% ($P < 0.001$), 4.9% ($P < 0.001$), and 3.2% ($P < 0.001$) and SM by 4.9% ($P < 0.001$), 5.8% ($P < 0.001$), and 2.9% ($P < 0.001$) in the NN, IT, and shaft, respectively, after 12 months. BR significantly decreased at 3 months after administration in the IT and at 6 months after administration in the NN and shaft. BR significantly decreased by −3.0% ($P < 0.001$), −4.2% ($P < 0.001$), and −1.4% ($P = 0.028$) in the NN, IT, and shaft, respectively, after 12 months.

As seen for BMD and the geometry indices, the effects of minodronic acid hydrate on the bone strength indices most significantly appeared in the IT, followed by the NN, and then the shaft.

Discussion

The present study demonstrates that minodronic acid hydrate, a new bisphosphonate, improves bone strength indices in the proximal femur in patients with osteoporosis. The comparison of femoral geometry and bone strength indices before and after administration allows investigation of the mechanism of drug action in the prevention of fracture. Specifically, most changes in the indices for bone density, geometry, and strength were observed in all

Table 3 Femoral BMD, geometry, and strength indices at baseline and after the administration of minodronic acid hydrate for 12 months

	Baseline	12 months	*P* value
Narrow neck (NN)			
BMD (g/cm^2)	0.661 ± 0.091	0.681 ± 0.092	<0.001
CSA (cm^2)	1.933 ± 0.237	1.993 ± 0.229	<0.001
Outer diameter (OD) (cm)	3.085 ± 0.231	3.088 ± 0.231	0.812
Endocortical diameter (ED) (cm)	2.834 ± 0.250	2.829 ± 0.253	0.345
Cortical thickness (CoTh) (cm)	0.126 ± 0.018	0.130 ± 0.019	<0.001
CSMI (cm^4)	1.585 ± 0.337	1.650 ± 0.327	<0.001
Section modulus (SM) (cm^3)	0.899 ± 0.154	0.937 ± 0.141	<0.001
Buckling ratio (BR)	14.389 ± 2.895	13.922 ± 2.874	<0.001
Intertrochanter (IT)			
BMD (g/cm^2)	0.639 ± 0.099	0.664 ± 0.098	<0.001
CSA (cm^2)	3.135 ± 0.488	3.250 ± 0.485	<0.001
Outer diameter (OD) (cm)	5.162 ± 0.310	5.150 ± 0.307	0.672
Endocortical diameter (ED) (cm)	4.612 ± 0.331	4.581 ± 0.329	0.096
Cortical thickness (CoTh) (cm)	0.275 ± 0.044	0.284 ± 0.046	<0.001
CSMI (cm^4)	7.718 ± 1.811	8.047 ± 1.798	<0.001
Section modulus (SM) (cm^3)	2.520 ± 0.531	2.652 ± 0.525	<0.001
Buckling ratio (BR)	11.464 ± 2.327	10.956 ± 2.172	<0.001
Shaft			
BMD (g/cm^2)	1.204 ± 0.149	1.222 ± 0.150	<0.001
CSA (cm^2)	3.080 ± 0.362	3.141 ± 0.370	<0.001
Outer diameter (OD) (cm)	2.697 ± 0.200	2.709 ± 0.205	0.014
Endocortical diameter (ED) (cm)	1.817 ± 0.297	1.813 ± 0.304	0.745
Cortical thickness (CoTh) (cm)	0.440 ± 0.072	0.448 ± 0.072	<0.001
CSMI (cm^4)	2.209 ± 0.473	2.278 ± 0.492	<0.001
Section modulus (SM) (cm^3)	1.570 ± 0.244	1.616 ± 0.255	<0.001
Buckling ratio (BR)	3.278 ± 0.694	3.228 ± 0.693	0.026

Each value is shown as the mean ± SD

BMD bone mineral density, *HSA* hip structure analysis, *CSMI* cross-sectional moment of inertia

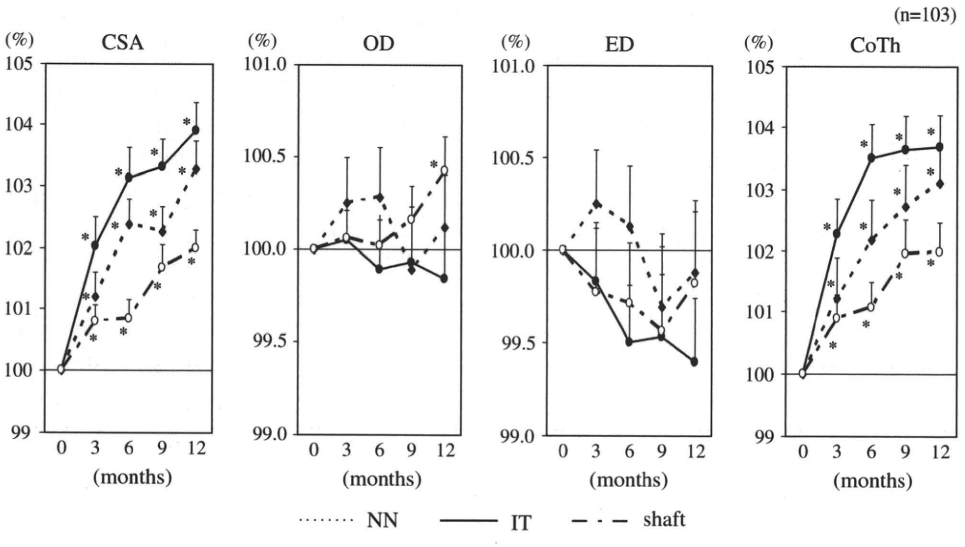

Fig. 2 Percentage changes from baseline of the cross-sectional area, outer and endocortical diameters, and cortical thickness of the femoral head, trochanter, and shaft at 3, 6, 9, and 12 months of treatment. Data are shown as means ± SE ($n = 103$); *$P < 0.05$ versus baseline (Wilcoxon test). *CSA* cross-sectional area, *OD* outer diameter, *ED* endocortical diameter, *CoTh* cortical thickness, *NN* narrow neck, *IT* intertrochanter

femoral regions starting from an early stage (3–6 months) after administration of minodronic acid hydrate. The strongest effect occurred in the femoral trochanteric region as a result of the dominant action of the bisphosphonate on cancellous bone. No significant increase in the outer diameter, which is reported to typically occur with aging, was observed during the 12-month follow-up period; in contrast, it is of interest that a slight decrease in

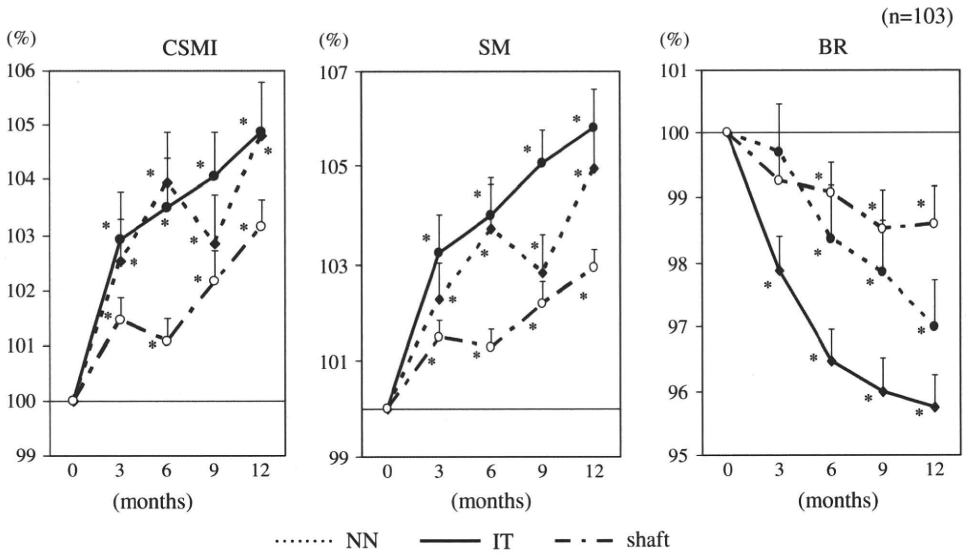

Fig. 3 Percentage changes from baseline of bone strength indices (CSMI, SM, BR) of the femoral neck, trochanter, and shaft at 3, 6, 9, and 12 months of treatment. Data are shown as means ± SE ($n = 103$); *$P < 0.05$ versus baseline (Wilcoxon test). *CSMI* cross-sectional moment of inertia, *SM* section modulus, *BR* buckling ratio, *NN* narrow neck, *IT* intertrochanter

endocortical diameter (−0.1% in the NN, −0.6% in the IT, and −0.2% in the shaft) was observed, which is generally thought to increase with aging. This change might be caused by an inhibition of endocortical resorption by minodronic acid hydrate, resulting in a significantly increased CSA (3.3% in the NN, 3.9% in the IT, and 2.0% in the shaft) and CoTh (3.1% in the NN, 3.7% in the IT, and 2.0% in the shaft). The bone strength parameters calculated by the HSA algorithm include the cortical CSA as an index of strength against axial compressive load, CSMI and SM as strength indices against bending load, and BR as an index for predisposition to local buckling caused by thinned cortices. In the present study, we found a significant change in CSMI, SM (4.9% in the NN, 5.8% in the IT, and 2.9% in the shaft at 12 months), and BR (−3.0% in the NN, −4.2% in the IT, and −1.4% in the shaft at 12 months). These improvements were observed at 3 months after administration of minodronic acid hydrate, suggesting that potent inhibition of endocortical resorption results in an increase in cortical thickness so as to sustain or improve bone strength. These effects of the bisphosphonate appeared in high metabolic turnover regions such as the cancellous and endocortical bone.

A clinical study based on HSA-based assessment of the effects of alendronate (ALN) or estrogen (EST) reported the effects on SM for IT and NN to be 9.1 and 7.3%, respectively, with ALN; 5.8 and 6.9%, respectively, with EST; and 3.4 and 3.2%, respectively, with a placebo [17]. BR increased with the placebo, whereas no change or a decrease occurred with ALN or EST ($P < 0.05$). This study was performed in 373 women over the age of 65 years for 3 years. In the Fosamax Actonel Comparison Trial (FACT study), ALN and risedronate (RIS) were administered once weekly (70 and 35 mg/week, respectively) for 2 years, and HSA-based assessment showed that both bisphosphonates improved bone geometry [18]. ALN and RIS increased SM by 6–7% and approximately 4%, respectively, while ALN decreased BR by approximately 2% and RIS increased BR by approximately 1% in the narrow neck. It is difficult to compare the results in the present study with previous studies on bisphosphonates because of differences in the race and age of the subjects, the criteria for diagnosis of osteoporosis in patients with low bone density, and dose and administration method (daily or weekly). However, prominent effects of minodronic acid hydrate were observed that were similar to those reported for other bisphosphonates.

The current study has the limitation that no control group was included; however, the multicenter design should help to limit any bias in the findings. Furthermore, several previous papers have reported there are no positive effects on HSA parameters in the placebo group receiving calcium supplementation at 1 year [19–22]. Data were collected for 1 year, and the effects of the agent may increase over a 2-year time-course based on changes in bone biomarkers and bone density [10, 11]. The beneficial effect on hip BMD is thought to be an important preventative factor for not only hip fracture but also vertebral fractures [23], and the early significant effects on hip BMD and HSA parameters are thought to be important for the near term as well as a longer-term preventive effect. The next few years of follow-up, to observe the incidence of hip fracture in the HSA-based assessment of intervention studies, will ultimately reveal whether geometry derived by HSA effectively serves as a surrogate marker of hip fracture. In fact, a review of reports using HSA in evaluation of the efficacy of antiosteoporotic agents [17–22] suggests that potent increase in bone strength indices derived from HSA does have an association with reduction in the incidence of hip fracture [24–26].

Previous HSA-based studies of bisphosphonate effects on the proximal femur have only included Caucasian patients. As there may be a racial difference in hip geometry, bone size, and bone density, HSA results might differ among races. Only one study using HSA assessment in Japanese patients has been performed to investigate the effects of an antiosteoporotic agent (raloxifene) [27], and therefore our study provides the first multicenter evidence of the efficacy of a bisphosphonate on hip geometry in a Japanese population. We conclude that minodronic acid hydrate may prevent hip fracture by inhibiting aging-related endocortical resorption, resulting in increased cortical thickness and improved bone strength indices in the proximal femoral region.

Acknowledgments We express our gratitude to Dr. Tatsushi Tomomitsu, the Department of Nuclear Medicine, Kawasaki Medical School, for his help with the HSA-based assessment. Pacific Edit reviewed the manuscript before submission.

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Bone 48 (2011) 627–630

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Age-related changes in bone density, geometry and biomechanical properties of the proximal femur: CT-based 3D hip structure analysis in normal postmenopausal women

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ARTICLE INFO

Article history:
Received 24 September 2010
Revised 5 November 2010
Accepted 9 November 2010
Available online 16 November 2010

Edited by: Toshio Matsumoto

Keywords:
Hip geometry
Bone mineral density (BMD)
Computed tomography (CT)
Osteoporosis

ABSTRACT

The geometry as well as bone mineral density (BMD) of the proximal femur contributes to fracture risk. How and the extent to which they change due to natural aging is not fully understood.

We assessed BMD and geometry in the femoral neck and shaft separately, in 59 normal Japanese postmenopausal women aged 54–84 years, using clinical computed tomography (CT) and commercially available software, at baseline and 2-year follow-up. This system detected significant reductions over the 2-year interval in total BMD (%change/year = -0.900 ± 0.257, $p<0.0005$), cortical cross-sectional area (CSA) (-0.800 ± 0.423%/year, $p<0.05$) and cortical thickness (-1.120 ± 0.453%/year, $p<0.01$) in the femoral neck. In the femoral shaft, cortical BMD decreased significantly (-0.642 ± 0.188%/year, $p<0.005$). Regarding biomechanical parameters in the femoral neck, the cross-sectional moment of inertia (CSMI) and section modulus (SM) decreased (-1.38 ± 3.65%/year, $p<0.01$ and -1.37 ± 2.96%/year, $p<0.005$) and the buckling ratio (BR) increased significantly (1.48 ± 4.81%/year, $p<0.05$), whereas no changes were found in the femoral shaft.

The distinct patterns of age-related changes in the geometry and biomechanical properties in the femoral neck and shaft suggest that improved geometric measures are possible with the current non-invasive method using clinical CT.

Introduction

The incidence of vertebral fracture increases linearly with aging and correlates closely with a decline in spinal bone mineral density (BMD). The incidence of hip fracture, on the other hand, increases exponentially with advancing age, although hip BMD decreases linearly, suggesting that age-related factors other than BMD contribute substantially to the fragility of the proximal femur. Declining BMD and geometry of the proximal femur, as well as an increase in the incidence of fall are believed to underlie the increased risk of hip fracture in the elderly [1–3]. Non-invasive techniques can provide bone structural information, beyond simple bone densitometry, to help assess fracture risk.

The aging skeleton is characterized by a deterioration of the trabecular microstructure, increased endocortical bone resorption, decreased cortical bone density or increased cortical porosity, and increased periosteal bone formation [4]. In postmenopausal women, the rate of periosteal bone formation declines to a greater extent, while endosteal bone resorption is more elevated, compared with age-matched men. However, the natural course of these cortical changes with aging has not been well elucidated, and how faithfully non-invasive methods can detect these changes over time is also unknown.

Age-related changes in the cortical bone of the femoral neck as well as the shaft have been investigated by means of histology or computed tomography (CT) images. Although cross-sectional analyses of age-related changes in hip geometry have been reported using clinical CT [5,6] or dual X-ray absortiometry (DXA) [7], there have been no reports of age-related changes in geometry along with BMD in the femoral neck and shaft simultaneously, and which also followed the changes longitudinally in the same subjects.

Here we report the results of longitudinal as well as cross-sectional analyses of clinical CT on age-related changes in BMD, geometry and biomechanical properties of the proximal femur, neck and shaft separately, in the same cohort of healthy postmenopausal Japanese women. The information provided in this study may form the basis for future investigation into how osteoporosis intervention impacts the biomechanical properties along with the structure of the femoral neck and shaft.

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doi:10.1016/j.bone.2010.11.007

Subjects and methods

Subjects

The subjects were 59 postmenopausal women who had volunteered to have spinal BMD measurements taken annually by DXA [8] and agreed to participate in the current prospective CT study. They were aged 54–84 (67.0 ± 7.4) years of age and had no physical problems in daily life. Their BMD values in the lumbar spine and the proximal femur were above 70% of the Japanese young adult mean [9]. None of the participants had any prevalent radiological vertebral fracture based on the semi-quantitative method of Genant [10], or any history of fragility fractures of hip, radius and humerus. They were enrolled in hip CT studies in August 2006 or December 2006 at the baseline and in August 2008 or December 2008 for the follow-up study. Table 1 summarizes their demographic features.

The study was reviewed and approved by the appropriate Internal Review Boards at Nagasaki University Hospital. Written informed consent to participate was obtained from all subjects.

CT data acquisition

A multi-detector-row CT (MDCT) scanner (Aquilion16, Toshiba Medical Systems Corporation, Tokyo, Japan) at Nagasaki University Hospital was used, and the same X-ray scan conditions, including kVp, mAs and beam pitch, were employed for the baseline and follow-up studies. The average number of slices was 690 ± 33.3. CT scanning of the proximal femur was performed twice during a 2-year period (1.99 ± 0.01 years). The reference phantom which was scanned simultaneously, was a B-MAS200 (Fujirebio Inc., Japan) containing hydroxyapatite at 0, 50, 100, 150 and 200 mg/cm^3. The scanning conditions were adjusted to 120 kV, 250 mA and a reconstruction thickness of 0.5 mm, and the spatial resolution was 0.625 × 0.625 mm. The radiation dose was 19.7 mGy at maximum, as shown by the CTDIvol [3].

The subjects were scanned in the supine position, with the reference phantom placed under them so as to cover a region from the top of the acetabulum to 5 cm below the bottom of the lesser trochanter in both hip joints. A bolus bag was placed between the subject and the CT calibration phantom. The CT scanner table height was set to the center of the greater trochanter.

Analysis of BMD and geometry data obtained by CT

The BMD and geometry data of the proximal femur were analyzed by a radiologist (M.I.), using commercial software (QCT PRO; Mindways, Austin, USA). The exact 3-D rotation of the femur and the threshold setting for defining the bone contours appeared to be the two most critical steps to ensure the accuracy and reproducibility of the automated procedure. The femoral neck axis was identified visually and automatically with the "Optimize FN Axis" algorithm. The CT values were converted to BMD scale using a solid reference phantom. QCT BIT processing was then performed with a fixed bone threshold for inner cortical separation, which was set to 350 mg/cm^3 for all of the CT images.

The BMD and the areas (CSA) of total and cortical regions of the cross-sectional femoral neck, as well as cortical thickness and the cortical perimeter, were calculated using QCT PRO software. Trabecular BMD and CSA were calculated on the basis of the total and cortical BMD and CSA. Cortical thickness was measured as the average of the whole cortex [11]. In the cross-sectional femoral shaft, the cortical BMD, CSA and perimeter were determined. As biomechanical parameters, the cross-sectional moment of inertia (CSMI), section modulus (SM) and buckling ratio (BR) were obtained for the femoral neck, and CSMI and SM for the femoral shaft. SM is a parameter calculated as the CSMI divided by the distance to the center of mass (CM) (d_{max}). BR was calculated as the d_{max} divided by the average cortical thickness in this study. They are derived in a manner intended to be consistent with the DXA-based HSA method implemented by Tom Beck [12].

The reproducibility (% coefficient of variation) of the analysis by the QCT PRO program was calculated using five repeated analyses with visual matching each time from seven healthy subject CT data sets from this study without visible artifact; coefficient of variation (%) as the root mean square standard deviation divided by the mean, for the total BMD was 1.49%, cortical BMD 2.63%, total mass 1.12%, total area 1.71%, cortical area 2.11%, cortical perimeter 2.11%, and cortical thickness 3.58% for FN. In the femoral shaft, the CV% was 0.52% for cortical BMD, 0.77% for cortical CSA, 1.10% for perimeter, 2.19% for CSMI and 1.00% for SM.

The high correlation ($r = 0.84$ to 0.98; $p < 0.0001$ in all) between the baseline and follow-up measurements (shown in Table 3) indicates the high reproducibility of the measurements using clinical CT and of the analysis performed by this application.

Statistical analysis

In the cross-sectional study, we calculated a linear regression as a function of age, and the correlation coefficients (r). In the longitudinal study, the follow-up data was compared with the baseline data using t-test, and also for each case, the average percent (%) changes of the follow-up data from the baseline were calculated, and the data obtained in the femoral neck and the femoral shaft were compared using t-test. These are expressed as average values (mean) and standard deviations (SD), assuming a two-sided level of significance of 5% ($p < 0.05$). These analyses were performed using SPSS version 11.

Table 1
Demographics of participants.

		Mean	SD
Age	years	67.0	7.4
Body weight	kg	54.7	14.2
Body height	cm	150.2	14.3
Age at menopause	years	50.4	4.1
Femoral neck BMD	g/cm^2	0.752	0.095
T-score	1	−1.2	0.8
Z-score	1	0.8	0.7

BMD, bone mineral density measured by DXA.

Results

Correlation between age and BMD/geometry/biomechanical properties at the baseline

Table 1 summarizes the demographic features of the 59 participants. They were healthy postmenopausal Japanese women who volunteered this study, and their ages ranged over 30 years, from 54 to 84 (67.0 ± 7.4) years. They did not have any fractures or a diagnosis of osteoporosis according to the BMD criteria of Japanese Society for Bone and Mineral Research (JSBMR) [9]. As a first step to obtaining information on the natural course of structural changes with advancing age, we examined if there were any correlations between the ages of the subjects and BMD/geometry/biomechanical properties of the proximal femur at baseline.

As shown in Table 2, at the femoral neck, the total BMD (−3.07 g/cm^3/year; $r = 0.39$, $p < 0.005$) and total bone mass (−0.019 g/year; $r = 0.47$, $p < 0.0005$) negatively correlated with age, while total CSA exhibited no correlation (0.008 cm^2/year; $r = 0.08$, ns). Cortical CSA (−0.028 cm^2/year; $r = 0.51$, $p < 0.0001$), cortical bone mass (−0.019 g/year; $r = 0.46$, $p < 0.0005$) and cortical thickness (−0.025 mm/year; $r = 0.46$, $p < 0.0005$) also negatively correlated with age, while cortical BMD exhibited no

Table 2
Correlations between age and BMD, geometry and biomechanical properties at the baseline.

Measurement		Change/year	Unit	r	p
FN BMD/geometry					
Total BMD		−3.065	mg/cm³/year	0.39	<0.005
Total CSA		0.008	cm²/year	0.08	ns
Total bone mass		−0.019	g/year	0.47	<0.0005
Cortical BMD		−0.997	mg/cm³/year	0.15	ns
Cortical CSA		−0.028	cm²/year	0.51	<0.0001
Cortical bone mass		−0.019	g/year	0.46	<0.0005
Cortical thickness		−0.025	mm/year	0.46	<0.0005
Perimeter		0.014	mm/year	0.23	<0.05
FS BMD/geometry					
Cortical BMD		−1.965	mg/cm³/year	0.29	<0.01
Cortical bone area		−0.011	cm²/year	0.26	<0.05
Perimeter		0.007	mm/year	0.10	ns
Biomechanical property					
FN	CSMI	−0.008	cm⁴/year	0.37	<0.005
	SM	−0.006	cm³/year	0.41	<0.005
	BR	0.104	1/year	0.51	<0.0001
FS	CSMI	−0.005	cm⁴/year	0.17	ns
	SM	−0.005	cm³/year	0.28	<0.05

FN, femoral neck; FS; femoral shaft; BMD, bone mineral density; CSA, cross-sectional area; CSMI, cross-sectional moment of inertia; SM, section modulus; BR, buckling ratio.

correlation (−0.997 mg/cm³/year; $r=0.15$, ns). The bone perimeter exhibited a positive correlation with age (0.014 mm/year; $r=0.23$, $p<0.05$).

At the femoral shaft, cortical BMD (−1.965 mg/cm³/year; $r=0.29$, $p<0.001$) and cortical CSA (−0.011 cm²/year; $r=0.26$, $p<0.05$) negatively correlated with age, while the bone perimeter did not exhibit any correlation.

Regarding the biomechanical properties shown in Table 2, CSMI (−0.008 cm⁴/year; $r=0.37$, $p<0.005$) and SM (−0.006 cm³/year; $r=0.41$, $p<0.005$) at the femoral neck exhibited a significant negative correlation with age. These changes were smaller at the femoral shaft (−0.005 cm⁴/year; $r=0.17$, ns for CSMI, −0.005 cm³/year; $r=0.28$, $p<0.05$ for SM). BR at the femoral neck displayed a positive correlation with age (0.104/year; $r=0.51$, $p<0.0001$) (Table 2).

Longitudinal changes at 2-year follow-up

Next, we re-examined all of the participants after 2 years to address whether the current CT-based HSA detected parameter changes over the 2-year interval. Table 3 summarizes the average values at baseline and the 2-year follow-up for the densitometric and geometrical measurements as well as the biomechanical properties. In each case, the correlations of the changes from the baseline were high, ranging from $r=0.84$ to 0.98 (all; $p<0.0001$).

Importantly, the current CT system detected significant decreases from baseline in total BMD (−0.900 ± 0.257%/year; $p<0.0005$), cortical CSA (−0.800 ± 0.423%/year; $p<0.05$) and cortical thickness (−1.120 ± 0.453%/year; $p<0.01$) at the femoral neck, and also a decrease in the cortical BMD of the femoral shaft (−0.642 ± 0.188%/year; $p<0.005$) (Table 3). These changes in the longitudinal analysis were consistent with the results of the cross-sectional analysis presented above (Table 2).

Our system did not detect any significant changes in the biomechanical properties of the femoral shaft (Table 3). However, a worsening of all the biomechanical properties of the femoral neck the 2-year period was observed; CSMI (−1.38 ± 3.65%/year; $p<0.01$) and SM (−1.37 ± 2.96%/year; $p<0.005$) decreased, and BR increased from the baseline (1.48 ± 4.81%/year; $p<0.05$) (Table 3).

Table 3 also summarizes the results of the longitudinal analysis by comparing the average% changes at the femoral neck versus the shaft. The average% change in cortical BMD was significantly higher in the femoral shaft than in the neck (0.081 ± 0.274%/year, ns in FN, and −0.642 ± 0.188%/year, $p<0.005$ in FS). The average% decreases in the CSMI and SM were significantly greater in the femoral neck (−1.38 ± 3.65%/year, $p<0.01$ for CSMI and −1.37 ± 2.96%/year, $p<0.05$ for SM) than in the shaft (−0.16 ± 2.30%/year, ns for CSMI and −0.32 ± 2.43%/year, ns for SM) (Table 3).

Discussion

It is widely recognized that aging has a substantial impact on the geometry of the proximal femur [4], and data on age-related changes in the hip geometry not only provides crucial insight into the pathogenesis of hip fracture, but also should help form the basis for

Table 3
Longitudinal changes in BMD, geometry and biomechanical properties during the 2-year follow-up.

	Measurement	Unit	Baseline	Follow-up	%change/year	p	p (vs. FS)	Correlations (baseline and follow-up)
FN BMD/geometry								
	Total BMD	mg/cm³	335.7 ± 58.7	329.8 ± 58.5	−0.900 ± 0.257	<0.0005	-	0.98
	Total CSA	cm²	5.75 ± 0.74	5.78 ± 0.84	0.417 ± 0.424	ns	-	0.90
	Total bone mass	g	1.89 ± 0.30	1.86 ± 0.28	−0.613 ± 0.390	ns	-	0.92
	Cortical BMD	mg/cm³	687.9 ± 48.4	688.6 ± 47.7	−0.081 ± 0.274	ns	<0.05	0.84
	Cortical CSA	cm²	1.96 ± 0.41	1.92 ± 0.37	−0.800 ± 0.423	<0.05	ns	0.94
	Cortical bone mass	g	1.34 ± 0.31	1.32 ± 0.29	−0.776 ± 0.529	ns	-	0.94
	Cortical thickness	mm	1.83 ± 0.40	1.78 ± 0.36	−1.120 ± 0.453	<0.01	-	0.94
	Perimeter	mm	5.78 ± 0.50	5.78 ± 0.56	0.024 ± 0.316	ns	ns	0.88
FS BMD/geometry								
	Cortical BMD	mg/cm³	1022.6 ± 52.5	1011.5 ± 49.9	−0.642 ± 0.188	<0.005	-	0.86
	Cortical CSA	cm²	3.58 ± 0.31	3.56 ± 0.32	−0.752 ± 0.499	ns	-	0.97
	Perimeter	mm	8.78 ± 0.48	8.80 ± 0.51	0.114 ± 0.413	ns	-	0.88
Biomechanical property								
FN	CSMI	cm⁴	0.613 ± 0.156	0.597 ± 0.159	−1.38 ± 3.65	<0.01	<0.01	0.96
	SM	cm³	0.448 ± 0.105	0.437 ± 0.108	−1.37 ± 2.96	<0.005	<0.05	0.97
	BR	1	7.06 ± 1.67	7.20 ± 1.61	1.48 ± 4.81	<0.05	-	0.94
FS	CSMI	cm⁴	1.304 ± 0.236	1.298 ± 0.231	−0.16 ± 2.30	ns	-	0.96
	SM	cm³	1.082 ± 0.142	1.075 ± 0.139	−0.32 ± 2.43	ns	-	0.93

Data are shown as mean ± SD. FN, femoral neck; FS, femoral shaft; BMD, bone mineral density; CSA, cross-sectional area; CSMI, cross-sectional moment of inertia; SM, section modulus; BR, buckling ratio; p value, significance in %change/year of parameters; p (vs. FS), significance in %change/year in FN against %change/year in FS; p* value, significance in correlation between baseline and follow-up measurements.

evaluating and understanding the efficacy of intervention. Important questions that remain unanswered include the extent to which age-related geometry changes actually occur, skeletal sites and time scale of these changes, whether they can be detected by non-invasive techniques, and how long an interval is required to demonstrate the clinical efficacy of a certain intervention to prevent or reverse such changes. Practically, since most clinical trials are terminated within 3 years, it is critically important to know whether the effects of any intervention on age-related changes in geometry can be detected non-invasively within the time scale of 2–3 years.

There has been no report to our knowledge on the demonstration of age-related and/or skeletal site-specific changes in the 3D geometry of the proximal femur. The results of our cross-sectional analysis by CT are qualitatively similar to those obtained in a previous DXA-based HSA in a similar population of postmenopausal Japanese women [13]. However, the % changes with aging in the biomechanical parameters such as SM and BR are larger in the current CT-based analysis than in the previous DXA-based study. In this respect, the 3D d_{max} calculation may have contributed to the increased sensitivity to the age-related changes in SM and BR in the current study.

According to the previous DXA-based HSA studies that analyzed the effects of anti-osteoporosis drugs on the geometry [14–16], distinct effects on the femoral neck and shaft were observed. In the current study using non-invasive CT scanning of the proximal femur, all of the biomechanical parameters, CSMI, SM and BR, worsened significantly with advancing age in the femoral neck, while those in the femoral shaft did not change.

The current study using a CT-based system demonstrated that cortical BMD was maintained at a higher level in the femoral shaft than in the femoral neck from the period of early post-menopause through advanced age, and that the decline in cortical BMD was much greater in the femoral shaft than the femoral neck (Table 3). It is counterintuitive that the femoral shaft would maintain a higher BMD throughout this period but nevertheless exhibit a larger bone loss than the femoral neck, since in comparison with the cortex of the femoral shaft [17], the femoral neck is thought to suffer from high cortical porosity. This may reflect a partial volume effect in measuring cortical BMD and thickness by CT, and higher resolution CT or more detailed histological analysis of the cortical bone in femoral neck and shaft may be required to validate the current findings.

The current system did not detect any significant change in the cortical BMD of the femoral neck, but detected changes in cortical thinning at the same site (Table 3). The border between the cortical and cancellous compartments becomes less obvious with aging, and the progression of cortical porosity in the endocortical region makes it difficult to distinguish it from the thinning of the cortex. Due to this limitation inherent in clinical CT, an alteration in cortical thickness, and not cortical bone density, may have been detected as an age-related change. Further efforts to improve the methodology of delineating the border between cortical and trabecular components accurately are thus required.

The findings that the bone perimeter and total CSA in the femoral neck did not change over a 2-year follow-up, while cortical CSA and thickness at the same site decreased significantly, imply that the current CT-based HSA was capable of detecting the progression of endocortical resorption, while the alteration in periosteal apposition rate, at least during this 2-year period, was too small to be detected. Taken together with the results of the cross-sectional analysis at baseline that both the bone perimeter and total CSA in the femoral neck correlated positively with age, a longer follow-up period would allow a determination of whether the periosteal bone formation continues at a slow pace.

In conclusion, the data presented in this study on age-related alterations in the geometry and biomechanical properties at distinct sites of the proximal femur should provide a basis for an improved understanding the pathogenesis of fracture, and also serve as a foundation for the design of new anti-fracture remedies in postmenopausal women.

Acknowledgments

The authors thank Toru Fukuda and Takako Shimogama (Division of Radiology, Nagasaki University Hospital) for technical assistance and Dr. Kyoji Ikeda (Department of Bone and Joint Disease, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan) for comments on the manuscript. This study was supported in part by a grant for the Promotion of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation (NIBIO) of Japan (06-31 to MI) and a Grant-in Aid for Scientific Research in Japan (22591344 to MI). Pacific Edit reviewed the manuscript before submission.

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CTによる骨質評価と骨折リスク

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Evaluation of Bone Quality and Fracture Risk Using Clinical CT

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臨整外 45：881～886，2010

Key words：コンピュータ断層撮影法(computed tomography)，骨ジオメトリー(bone geometry)，骨微細構造(microstructure)

CTによる骨質評価は構造特性の評価であり，骨ジオメトリーと海綿骨微細構造解析によって，骨折リスク予測や薬物効果評価に用いられるようになってきた．通常のCTが断面画像であるのに対して，多列検出器を有するmulti detector-row CT(MDCT)は容積画像を提供するので，三次元データに基づいて任意の断面での再構成画像を得ることができる．また高い空間分解能を提供するため，海綿骨微細構造解析の臨床における有用性も確認され，研究が進められている．今後テクノロジーの進歩による実用化を期待する．

はじめに

骨折リスクは骨密度のみで十分説明できないこと，また骨密度による薬効評価は感度が低いことが知られており，骨密度とともに骨質も考慮した骨評価が望まれている．しかしながら，現在臨床における骨質評価法はまだ十分に確立されていない．

X線computed tomography(CT)による骨質評価は構造特性の評価であり，骨ジオメトリーと海綿骨微細構造評価に用いられている．CTが骨構造描出に優れているのは，高い空間分解能と密度分解能を有し，三次元データを提供する点にある．

X線CT装置と骨解析

X線CTスキャナはX線照射した目的部分のX線減弱係数値の分布をコンピュータで算出して，多方向からの投影データをもとに内部構造を再構成したものである(図1)．

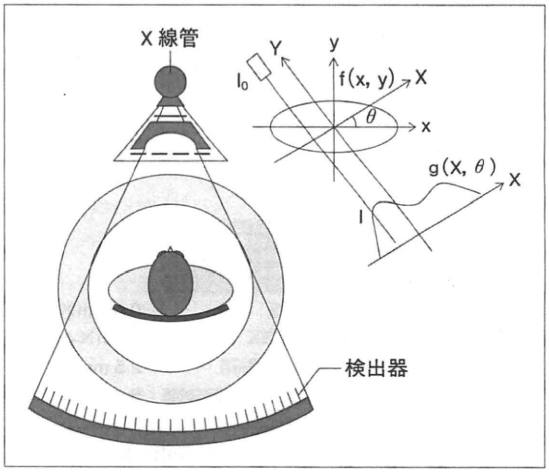

図1　CT(computed tomography；コンピュータ断層撮影法)の原理

CTの投影データはX線管球から照射され被写体を透過して減衰を受けたX線を検出器で測定した強度として与えられる．

上図のように被写体に固定した座標上で，被写体の線減弱係数の分布f(x，y)を求める．

多列検出器をもつCT装置は，multi detector-row CT(MDCT，図2)と呼ばれ，通常のCTが断面画像であるのに対して，MDCTは容積画像を

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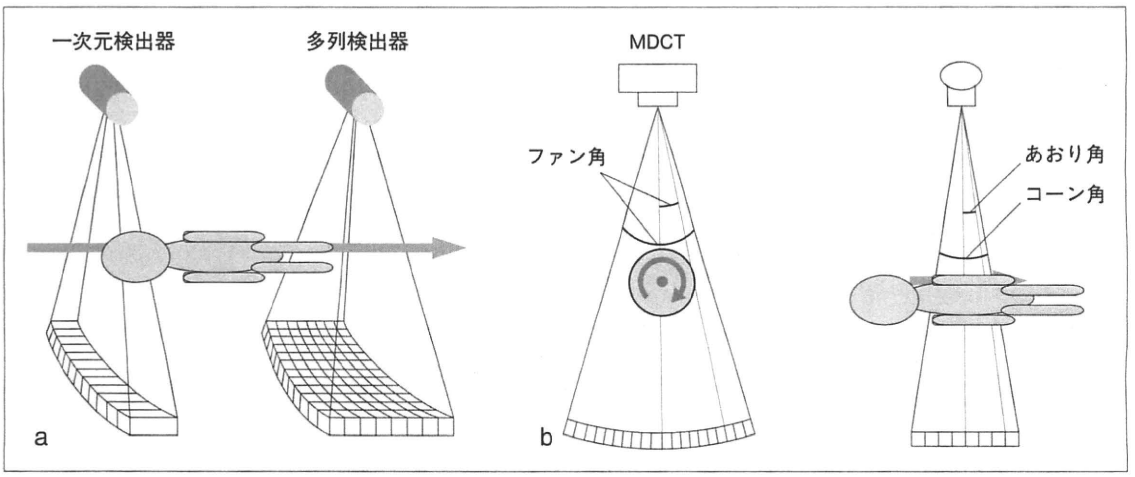

図2　MDCT(multi detector-row CT)とシングルスライス CT

a：シングルスライス CT は検出器が XY 平面に並び，Z 軸方向には 1 列である．Z 軸方向に検出器を多列にしたのが MDCT である．

b：MDCT の検出器は，XY 平面では，X 線管を中心にして配列している．Z 方向では平面に並ぶ．

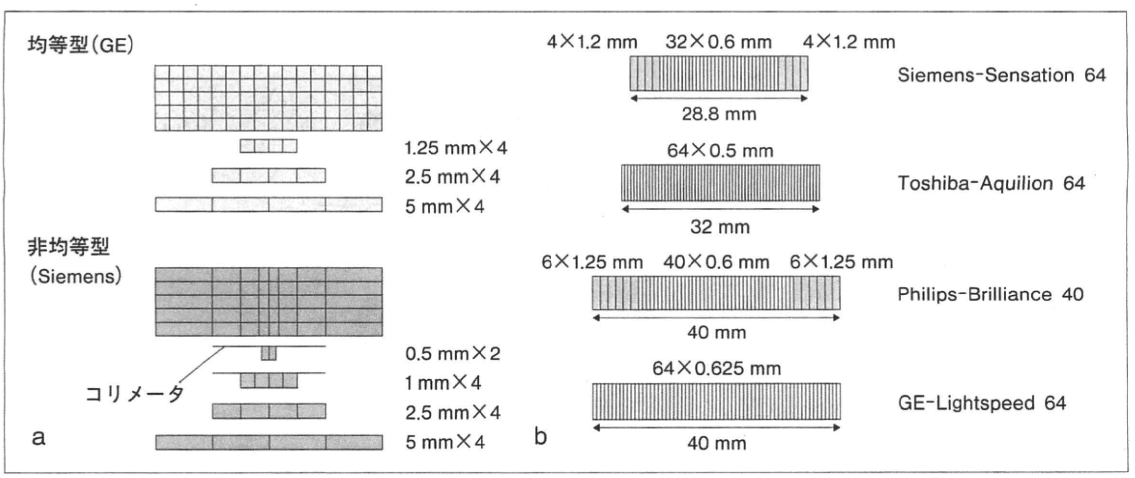

図3　MDCT(multi detector-row CT)と DAS(data acquisition system)

a：実際のスキャンでは多列検出器のうちの同時収集可能列数を選択して，DAS(data acquisition system；データ収集装置)で束ねて出力する．つまり，DAS によってスライス厚が異なる．例えば検出器の配列が均等型の場合では，1.25 mm の 4 列をデータ収集に使用する場合，2.5 mm の 4 列をデータ収集に使用する場合，5 mm の 4 列をデータ収集に使用する場合で，スライス厚が異なり分解能は異なる．

b：装置によって検出器の配列は均等型と非均等型がある．

提供するので，①高速スキャン，②広範囲の撮影，③薄いスライスの画像データ(thin slice data)を可能とした(図 3)．骨解析には循環器系の検査のような高速スキャンは要求されないが，骨評価における MDCT の有用な点は，①高い空間分解能を提供できる，②三次元データに基づいて，任意の断面での再構成画像を得ることである．図 3 に示すように DAS(data acquisition system)により，スライス厚やスキャン範囲と速度を調節できる．

Magnetic resonance(MR)も同様に三次元データを得ることができるが，皮質骨に関してのデータが得られないこと，撮像に時間がかかることなどの問題点がある．

海綿骨梁構造は棒状と板状の骨梁が連結しあって構成され，個々の骨梁の幅は 50～200 ミクロン，