experienced a 7.0 % LS BMD increase and postmenopausal women experienced a 7.8 % LS BMD increase [14]. However, none of these studies were specifically designed to directly compare the effects of teriparatide between men and women; therefore, it is unclear whether the effects of teriparatide were similar or different. In addition to these results, we believe that the magnitude of the LS BMD increase should be noted. Marcus et al. reported that similar absolute LS BMD increases were observed regardless of baseline BMD in postmenopausal women [15]. Although the relationship between baseline LS BMD and subsequent BMD increase in men is unclear, our results showed that the absolute LS BMD increase in men was similar to that in postmenopausal women regardless of baseline BMD. The noteworthy efficacy of teriparatide was demonstrated in this study because the percent LS BMD increase was dependent on the baseline LS BMD.

Regarding biochemical markers of bone turnover, Finkelstein et al. reported that serum PINP and serum NTX reached peak levels at 12 months after daily 37-μg teriparatide treatment in men [16]. Glüer et al. reported that serum PINP reached peak levels at 6 months in men [17]. This study showed that both the serum PINP level and uNTX level peaked at 4 months in men. The serum PINP level peaked at 4 months and the uNTX levels peaked at 8 months in postmenopausal women. The rapid increases in biochemical markers of bone turnover in men, which were similar to those in women, are consistent with an anabolic mode of action for teriparatide and indicate that teriparatide activated bone remodelling. The rapid and sustained gain in BMD during the 12-month teriparatide treatment implies a continuously positive coupling balance in favour of bone formation.

At the beginning of this study, we believed that the LS BMD increase was lower in men than in women because of differences in body weight. Neer et al. showed that teriparatide treatment resulted in significant dose-dependent increases in the BMD of the spine and hip [6]. However, our results showed that there was no significant difference in LS and FN BMD increases between in men and women by Mann–Whitney *U* test. Otherwise, there were different responses in the longitudinal percent FN changes between in men and women. The reason for different responses is unclear, but there might be a possibility of gender-specific difference or sample size effects (47 patients in men versus 334 patients in women). After referencing the differences in bone turnover markers, we speculate that there might be some differences between men and postmenopausal women in response to teriparatide. PINP response was similar in both groups, otherwise lower uNTX response was observed in men compared to women, which might produce an increased anabolic window and relatively higher BMD response in men.

This study has several limitations that should be considered when interpreting the results. First, because of the limited numbers of patients enrolled in this study, reduction in the fracture incidence could not be assessed. Second, we revealed the efficacy of teriparatide in BMD and identified biochemical markers of bone turnover, but we did not verify improvement in the microstructure of cortical and trabecular bone. Third, because of the observational and retrospective design of this study and the small number of subjects, the conclusions should be interpreted with caution. However, we believe that the results of this study are noteworthy because this is the first study to compare the efficacies of teriparatide treatment between men and women. Fourth, there were some differences in baseline characteristics between the men and women that, to some extent, depended on sex.

In conclusion, the study results in men showed that daily teriparatide treatment increased LS BMD and stimulated bone turnover. But there is a possibility of gender-specific difference in FN BMD response. Together with the previously reported results in women, the results provide evidence that teriparatide treatment is an effective option for osteoporosis in men.

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Conflicts of interest None.

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CLINICAL TRIAL

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Cortical Thickness of the Femur and Long-Term Bisphosphonate Use

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ABSTRACT

Femoral cortical thickening has been mentioned in reports of atypical subtrochanteric/femoral shaft (ST/FS) fractures, which are associated with long-term bisphosphonate (BP) use. However, whether thickening precedes BP use or results from BP use, as well as the role BPs may play in cortical thickening remain unclear. The purpose of this study was to investigate the relationship between cortical thickness and BP use. We enrolled 142 patients (mean age 79 years) who had taken BPs for more than 5 years, and enrolled 426 osteoporosis patients who had not used BPs as controls. We performed a case-control study of patients with long-term BP use and controls matched for age, sex, and levels of activities of daily living (ADLs) (1:3 ratio). On femoral radiographs, we measured femoral cortical thickness in three regions: 5 cm and 12.5 cm below the lesser trochanter and in the region of maximal cortical thickness. We compared cortical thicknesses between patients taking BP and controls and evaluated longitudinal changes in cortical thickness. There were no significant differences in cortical thickness between long-term BP users and controls. In addition, after further use of BP for a minimum of 1 year, we observed no significant differences in the changes in cortical thickness at any level of the femur. In conclusion, our study did not find evidence of cortical thickening at the ST/FS area of the femur with long-term BP use. © 2014 American Society for Bone and Mineral Research.

KEY WORDS: OSTEOPOROSIS; BISPHOSPHONATE; CORTICAL THICKNESS; ATYPICAL FEMORAL FRACTURE; CASE-CONTROL STUDY

Introduction

Bisphosphonates (BPs) are the most commonly prescribed medications for the treatment of osteoporosis. BPs significantly increase bone mineral density (BMD) and reduce the risk of vertebral, hip, and other nonvertebral fractures.[1] Recent studies have suggested a possible link between long-term BP use and atypical femoral fractures (AFFs) in the subtrochanteric/femoral shaft (ST/FS) areas.[2–6] Several reports have suggested that the decreased rate of bone turnover associated with the reduction in osteoclastic resorption leads to increased bone mineralization and causes the bone to become brittle.[7–9] These changes, combined with unrepaired microdamage, may lead to a long-term increase in the risk of fracture. These fractures have a transverse or short oblique orientation, may be noncomminuted or minimally comminuted, and are associated with hypertrophy of the cortex in the shaft.[2,4] Although AFFs are extremely rare, Gedmintas and colleagues conducted a systematic review and meta-analysis concerning the association of BP use with AFF and reported that there is a clear association between BP use and AFF, and the risk for AFF increases as the duration of BP use increases.[3]

The 2013 revised American Society for Bone and Mineral Research (ASBMR) case definition of AFF includes five major features and four minor features.[2] Although none of the minor features is required for the diagnosis of an AFF, minor features are sometimes associated with AFFs. Two of these features, localized periosteal thickening of the lateral cortex (major feature) and generalized increase in cortical thickness of the femoral diaphysis (minor feature), are suspected to exist before AFF. It has been postulated that this cortical thickening is the result of long-term BP use. A general increase in cortical thickness in the proximal femur was first observed by Lenart and colleagues[5] in femurs with AFFs. This led to the notion that BP use may induce changes in cortical thickness around the ST area of the femur, which may in turn predispose the bone to AFF. Burghardt and colleagues also reported an increased mean percentage of cortical thickness after 1 to 2 years of alendronate use.[10] Meanwhile, Unnanuntana and colleagues found no increase in proximal femoral cortical thickness in patients receiving prolonged alendronate treatment more than 5 years.[11] However, few studies have measured cortical thickness on radiographs including the FS area. In this study, we investigated radiographs from patients who had been treated with BPs for

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more than 5 years and osteoporotic patients who had not taken BPs and tried to determine whether long-term BP use leads to a change in cortical thickness in the ST/FS area of the femur.

Materials and Methods

Participants

In this case-control study, 142 patients who were long-term BP users (cases) and 426 osteoporotic patients without BP treatment (controls) were enrolled between December 2011 and March 2014. Patients who presented to our institution with osteoporotic fracture or low BMD at the lumbar spine or femoral neck (*T*-score 2.5) between December 2011 and March 2014 were recruited as controls. The 142 long-term BP users were all patients who were under follow-up at our institution. To avoid selection bias, which is a major disadvantage of a matched case-control study, we evaluated the maximum number of controls registered during the study period. A total of 620 potential control individuals were seen during the study period. The two groups were matched for age, sex, and ADLs. When we matched control patients with BP users, the age difference was limited to within ± 2 years. As a result, we could perform this case-control study with a patient/control ratio of 1:3.

For a type I error rate of 0.05 and a power of 0.8, with an expected prevalence of BP use of 10%, a difference in cortical thickness of 1.2 mm, and SD for cortical thickness of 2.6 mm, 49 cases would have been required. We computed the sample size required for a parametric test and added 15% because it is assumed that nonparametric tests may be required (57 cases).[12] Therefore, we estimated that 60 cases and 180 controls would be required. However, because we wanted to perform the analysis for lateral cortical stress fracture, we included all eligible patients with long-term BP use.

The protocol was in compliance with the ethical principles stated in the Declaration of Helsinki and was approved by the Ethics Committee of Tomidahama Hospital. Written informed consent was obtained from all patients.

Baseline measurements

We collected patients' baseline demographic data from registry records. The patients were stratified into low-, moderate-, and high-functioning levels according to the following criteria in reference to a previous report:[13] low functioning: requires assistance with all ADLs, lives with caregiver, and needs frame to mobilize or uses a wheelchair; moderate functioning: requires some assistance with ADLs, mobilizes with a handcart; and high functioning: requires no assistance with ADLs, functions independently, and able to mobilize a significant distance (ie, walks for exercise or can walk around supermarket). Patient details are shown in Table 1. The mean ages of the patients in the BP and control groups were 79 ± 9 years (mean [SD]) (range 52 to 99 years) and 79 ± 9 years (range 50 to 99 years), respectively. There were 129 female and 13 male patients in the BP group. Functioning levels were high in 114 patients, moderate in 20 patients, and low in 8 patients in the BP group.

Body weight, baseline *T*-scores at the lumbar spine and femoral neck, and serum phosphorus concentration did not differ significantly between the groups. Body mass index (BMI) and serum calcium concentration were higher in the BP group (Table 1), whereas height was lower in the BP group. The concentrations of bone turnover markers, urinary N-telopeptide (uNTX), and serum procollagen type I N-terminal propeptide (PINP) were lower in the BP group.

The minimum follow-up period for patients in the BP group was 5 years (mean 6.5 ± 1.1 years; range 5.0 to 12.0 years). The types of BPs used and the durations of use were as follows:

Table 1. Baseline Characteristics[a]

Variable	Bisphosphonate ($n = 142$)	Control ($n = 426$)	p Value[b]
Age (years)	79.1 ± 8.5 (52 to 99)	79 ± 8.5 (50 to 99)	0.70
Female sex	129	387	>0.99
Function levels			
High	114	342	>0.99
Moderate	20	60	>0.99
Low	8	24	>0.99
Race			
Asian	141	426	0.25
White	1	0	0.25
Height (cm)	149 ± 8 (130 to 171)	150 ± 7 (128 to 174)	0.03
Body weight (kg)	48 ± 9 (28 to 85)	47 ± 10 (23 to 85)	0.08
BMI (kg/m^2)	22 ± 3 (15 to 31)	21 ± 4 (12 to 34)	<0.01
T-score			
Lumbar spine	−1.7 ± 1.4 (−4.5 to 2.8)	−1.8 ± 1.3 (−4.7 to 3.2)	0.30
Femoral neck	−1.9 ± 0.9 (−4.8 to 0.6)	−2.0 ± 1.0 (−4.6 to 1.7)	0.10
Serum calcium (mg/dL)	9.6 ± 0.7 (6.7 to 11.8)	9.5 ± 0.6 (4.8 to 11.1)	0.03
Serum phosphorus (mg/dL)	3.5 ± 0.6 (1.9 to 5.3)	3.6 ± 0.6 (2.0 to 6.2)	0.09
Bone turnover markers			
Urinary NTX	24.1 ± 12.8 (5.2 to 75.4)	65.1 ± 41.5 (8.1 to 239.1)	<0.01
Serum PINP (μg/L)	26.4 ± 16.6 (7.6 to 99.7)	64.4 ± 33.5 (9.1 to 187.0)	<0.01

BMI = body mass index; NTX = N-telopeptide; PINP = procollagen type I N-terminal propeptide.
[a]Data are expressed as mean ± SD.
[b]Mann–Whitney *U* test, chi-square test, Fisher's exact test.

alendronate ($n = 132$; mean 6.6 ± 1.2 years; range 5.0 to 12.0 years) and risedronate ($n = 10$; mean 6.0 ± 1.0 years; range 5.0 to 7.5 years). We performed yearly X-ray evaluations in the patients who had used BPs for more than 5 years since 2011 as part of routine care. Baseline anteroposterior femoral radiographs were obtained for all patients. In addition, follow-up radiographs were obtained at least 1 year after baseline measurements (mean 1.4 ± 0.3 years; range 1.0 to 2.3 years) to evaluate changes in the longitudinal cortical thickness with BP treatment. We did not perform longitudinal evaluation in control groups.

Cortical thickness

The primary measures of cortical thickness included in the analysis were medial cortical thickness, lateral cortical thickness, total cortical thickness (medial plus lateral thickness), and the cortical thickness ratio. Cortical thickness was measured from radiographs at three regions: 5 cm below the lesser trochanter,[14] 12.5 cm below the lesser trochanter (midshaft area for almost all patients in this study), and at the position of maximal femoral cortical thickness (Fig. 1). Cortical thickness was reviewed independently by orthopedic surgeons or well-trained therapists who were blinded to patient characteristics. First, a line was drawn along the FS axis at the level of the greater trochanter. Thereafter, two pairs of four points were plotted on the FS at each level of measurement. Two points were placed on the outer surfaces of the femoral cortices; the other two were placed on the inner or medullary surfaces of the femoral cortices (Fig. 1, points B and C). Using the distance tool in the software of the picture archiving and communication system (PACS; Konica Minolta I-PACS FS with core software by V1.09R04, Tokyo, Japan), the FS and cortical diameters were obtained. Femoral diameter was defined as the distance between the outer surfaces of the femoral cortices (Fig. 1, line AD). All measurements were recorded in millimeters. The cortical thickness ratio was defined as the ratio of cortical thickness to the corresponding FS diameter. All radiographs were obtained by an experienced technician using a standardized protocol and uploaded using a computerized imaging system linked to PACS.

Differences in the ability of the observers to interpret femoral radiographs were investigated in advance. Nine physicians (three orthopedic surgeons and six therapists) belonging to the same faculty interpreted the radiographs. Physicians received training to standardize their approach to measuring cortical thickness using radiographs from 100 patients. We followed the recommendations of Loewen[15] for determining this sample size. The mean absolute difference and SD between measurements of intraobserver and interobserver variability were 0.2 ± 0.3 mm and 0.3 ± 0.3 mm, respectively. The correlation (Spearman) of the results from the two assessments was also calculated as a measure of agreement. The intraclass correlation coefficients (r) for intraobserver and interobserver reliability were 0.96 (range 0.96 to 0.99) and 0.98 (range 0.96 to 0.99), respectively. Accordingly, we assumed that there were no differences in the abilities of the different physicians to interpret radiographs with good reproducibility.

Biochemical markers of bone turnover

uNTX was measured by ELISA (Alere Medical Co., Ltd., Tokyo, Japan). The intra-assay and interassay % CV for uNTX are 6.6% and 6.5%, respectively.[16] Serum PINP was measured by a radioimmunoassay (Orion Diagnostica, Espoo, Finland) in the nonfasting state. The intraassay and interassay % coefficient of variation (CV) for PINP are 3.5% and 4.2%, respectively.[16] uNTX levels were measured in 132 patients (10 patients had difficulty providing samples for urine tests), and serum PINP levels were measured in all 142 patients of the BP group. In the control group, we did not perform uNTX and serum PINP tests in patients who had experienced a fracture within the previous 3 months. As a result, uNTX was measured in 285 patients and serum PINP was measured 312 patients in the control group.

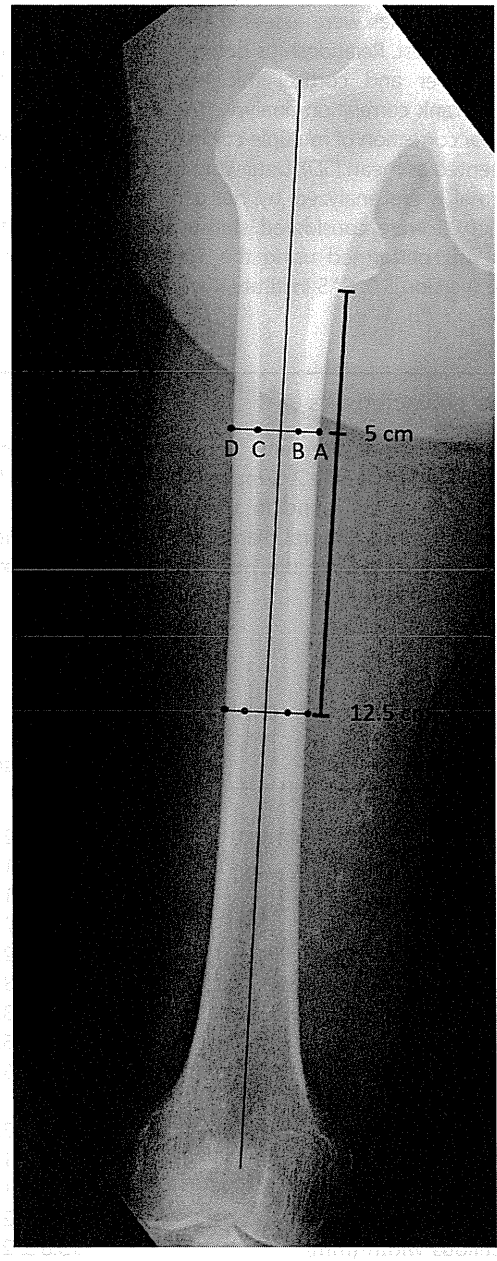

Fig. 1. Points at which cortical thickness was measured on anteroposterior radiographs of the femurs.

Data analysis

Differences in the FS diameter, cortical thickness, and cortical thickness ratio in the BP and control groups were assessed with the Mann–Whitney U-test. Longitudinal cortical thickness changes in

BP users were assessed with paired t tests. Differences in categorical variables were assessed with the chi-square test and Fisher's exact test. Relationships between biochemical markers of bone turnover and cortical thickness were evaluated by a Spearman rank correlation analysis. The Bonferroni method was applied for correction of multiple comparisons. Measurement data are presented as mean (SD). Data were tested for normality, and, if not normal, were analyzed by nonparametric methods. Any p values <0.05 were considered statistically significant. Statistical analysis was performed using the StatView statistical software package (version 5.0; SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

Baseline femoral measurements were compared between the BP and control groups (Table 2, Supporting Figs. S1, S2, and S3), and no differences were found in the cortical thickness, cortical thickness ratio, and femoral diameter at any level of the femur between the groups. We did not identify any cases of lateral cortical stress fracture.

Changes in longitudinal cortical thickness after additional BP use

Changes in the longitudinal cortical thickness were also evaluated in 98 of 142 patients who continued using BPs for another year and for whom subsequent radiographs could be obtained. As the Japanese Ministry of Health, Labour and Welfare approved daily teriparatide in October 2010, weekly terparatide in November 2011, and denosumab in March 2013, several patients who had received long-term BP treatment switched to these drugs. The reasons that subsequent radiographs were not obtained in some cases were as follows: 17 patients were lost to follow-up; less than 1 year had passed since the initial evaluation for 13 patients; 12 patients switched to other drugs; 1 patient finished osteoporosis treatment; and 1 patient relocated. After a minimum of 1 year of additional BP use, we observed no significant change in cortical thickness or the cortical thickness ratio at any level of the femur, but a significant change in the region of maximal femoral cortical thickness was observed according to the results of Wilcoxon signed-rank test (Table 3) and Bonferroni correction (data not shown).

Table 2. Femoral Measurements[a]

Variable	Bisphosphonate ($n=142$)	Control ($n=426$)	p Value[b]
CT 5 cm			
Femoral shaft diameter (mm)	28.8 ± 2.6 (22.9 to 36.0)	28.7 ± 2.5 (19.3 to 36.5)	0.97
Medial CT (mm)	6.7 ± 1.2 (3.2 to 9.9)	6.7 ± 1.3 (1.4 to 10.4)	0.57
Lateral CT (mm)	7.3 ± 1.2 (4.4 to 10.5)	7.2 ± 1.3 (2.0 to 12.0)	0.39
Total CT (mm)	14.0 ± 2.1 (7.6 to 19.3)	13.8 ± 2.4 (3.4 to 20.5)	0.51
Cancellous width (mm)	14.7 ± 2.1 (9.3 to 21.1)	14.8 ± 2.4 (9.4 to 24.7)	0.63
Medial CT to bone width (%)	23.4 ± 3.4 (11.5 to 32.6)	23.2 ± 4.0 (7.4 to 33.7)	0.50
Lateral CT to bone width (%)	25.4 ± 3.6 (14.5 to 36.5)	25.0 ± 4.2 (10.4 to 36.5)	0.35
Ratio total CT to bone width (%)	49.0 ± 5.7 (27.3 to 64.2)	48.2 ± 7.1 (17.8 to 65.0)	0.36
Cancellous width (%)	51.1 ± 5.8 (35.8 to 72.7)	51.8 ± 7.1 (35.0 to 82.4)	0.44
CT 12.5 cm			
Femoral shaft diameter (mm)	27.6 ± 2.4 (22.7 to 34.6)	27.6 ± 2.4 (21.2 to 37.1)	0.81
Medial CT (mm)	6.8 ± 1.1 (4.2 to 11.1)	6.8 ± 1.3 (1.9 to 11.4)	0.69
Lateral CT (mm)	7.0 ± 1.3 (4.1 to 10.8)	6.9 ± 1.4 (2.2 to 13.5)	0.89
Total CT (mm)	13.8 ± 2.2 (8.3 to 9.9)	6.7 ± 1.3 (1.4 to 10.4)	0.57
Cancellous width (mm)	13.8 ± 2.0 (9.3 to 19.5)	13.9 ± 2.3 (8.0 to 24.6)	0.73
Medial CT to bone width (%)	24.5 ± 3.3 (16.5 to 32.1)	24.5 ± 4.1 (8.9 to 35.4)	0.88
Lateral CT to bone width (%)	25.4 ± 3.9 (16.1 to 35.1)	25.1 ± 4.5 (10.0 to 38.9)	0.67
Ratio total CT to bone width (%)	49.9 ± 6.1 (32.5 to 63.3)	49.7 ± 7.6 (18.9 to 66.2)	0.87
Cancellous width (%)	50.0 ± 6.1 (36.6 to 67.5)	50.3 ± 7.6 (33.8 to 81.1)	0.82
Maximal femoral cortical thickness			
Location[c]	83.7 ± 11.3 (29.1 to 116.0)	84.9 ± 14.1 (11.2 to 134.8)	0.13
Femoral shaft diameter (mm)	28.0 ± 2.6 (22.6 to 35.4)	28.1 ± 2.5 (20.6 to 37.0)	0.25
Medial CT (mm)	7.0 ± 1.2 (4.5 to 11.3)	7.0 ± 1.3 (1.8 to 11.4)	0.69
Lateral CT (mm)	7.5 ± 1.3 (4.6 to 11.0)	7.5 ± 1.4 (2.6 to 13.7)	0.81
Total CT (mm)	14.5 ± 2.2 (9.1 to 21.8)	14.5 ± 2.4 (4.4 to 21.6)	0.86
Cancellous width (mm)	13.5 ± 1.9 (8.0 to 18.8)	13.6 ± 2.3 (7.9 to 22.7)	0.76
Medial CT to bone width (%)	25.1 ± 3.3 (17.3 to 34.6)	24.8 ± 4.0 (9.1 to 33.8)	0.39
Lateral CT to bone width (%)	26.6 ± 3.9 (17.5 to 38.3)	26.7 ± 4.3 (10.2 to 38.4)	0.94
Ratio total CT to bone width (%)	51.7 ± 5.9 (34.9 to 66.1)	51.5 ± 7.2 (21.7 to 67.9)	0.93
Cancellous width (%)	48.3 ± 5.9 (33.9 to 65.2)	48.6 ± 7.2 (32.1 to 78.6)	0.87

CT 5 cm = cortical thickness measured 5 cm below the lesser trochanter; CT 12.5 cm = cortical thickness measured 12.5 cm below the lesser trochanter.
[a]Data are expressed as mean ± SD.
[b]Mann–Whitney U test.
[c]Location refers to the distance from the lesser trochanter.

Table 3. Longitudinal Cortical Thickness Changes With Additional Bisphosphonate Use[a]

Variable	Baseline ($n = 98$)	Additional use ($n = 98$)	p Value[b]
CT 5 cm			
Femoral shaft diameter (mm)	28.8 ± 2.6 (22.9 to 36.0)	28.9 ± 2.6 (22.2 to 35.8)	0.40
Medial CT (mm)	6.9 ± 1.1 (4.1 to 9.5)	6.9 ± 1.1 (4.5 to 9.8)	0.97
Lateral CT (mm)	7.4 ± 1.3 (4.5 to 10.5)	7.4 ± 1.3 (4.1 to 10.7)	0.68
Total CT (mm)	14.3 ± 2.1 (9.5 to 19.3)	14.3 ± 2.1 (9.0 to 19.9)	0.79
Cancellous width (mm)	14.6 ± 1.9 (10.6 to 21.1)	14.6 ± 1.9 (10.8 to 20.9)	0.56
Medial CT to bone width (%)	23.7 ± 3.0 (16.3 to 31.0)	23.7 ± 2.7 (16.8 to 29.2)	0.80
Lateral CT to bone width (%)	25.6 ± 3.6 (14.5 to 36.5)	25.7 ± 3.8 (14.9 to 34.6)	0.91
Ratio total CT to bone width (%)	49.4 ± 5.3 (30.9 to 63.0)	49.3 ± 5.4 (31.7 to 60.2)	0.90
Cancellous width (%)	50.6 ± 5.3 (37.0 to 69.1)	50.7 ± 5.3 (39.8 to 68.3)	0.89
CT 12.5 cm			
Femoral shaft diameter (mm)	27.6 ± 2.3 (22.7 to 34.6)	27.5 ± 2.3 (22.2 to 34.5)	0.59
Medial CT (mm)	6.9 ± 1.1 (4.7 to 11.1)	6.8 ± 1.1 (4.1 to 10.7)	0.69
Lateral CT (mm)	7.1 ± 1.3 (4.5 to 10.8)	7.0 ± 1.3 (5.0 to 10.3)	0.74
Total CT (mm)	13.9 ± 2.2 (9.7 to 21.8)	13.9 ± 2.2 (10.1 to 21.0)	0.67
Cancellous width (mm)	13.6 ± 1.8 (10.1 to 18.4)	13.7 ± 1.9 (10.4 to 19.2)	0.88
Medial CT to bone width (%)	24.9 ± 3.1 (17.2 to 32.1)	24.5 ± 3.2 (14.9 to 31.3)	0.83
Lateral CT to bone width (%)	25.5 ± 3.9 (17.2 to 33.9)	25.5 ± 3.8 (18.1 to 33.9)	0.82
Ratio total CT to bone width (%)	50.4 ± 5.9 (36.1 to 63.3)	50.3 ± 5.9 (34.5 to 61.9)	0.79
Cancellous width (%)	49.6 ± 5.9 (36.6 to 64.0)	49.7 ± 5.9 (38.1 to 65.6)	0.78
Maximal femoral cortical thickness			
Location[c]	83.2 ± 10.5 (57.6 to 111.0)	80.5 ± 8.7 (64.7 to 109.1)	<0.01
Femoral shaft diameter (mm)	27.9 ± 2.6 (22.6 to 34.5)	28.2 ± 2.5 (21.8 to 34.8)	0.32
Medial CT (mm)	7.1 ± 1.2 (4.8 to 11.3)	7.1 ± 1.2 (4.3 to 11.6)	0.54
Lateral CT (mm)	7.4 ± 1.4 (4.9 to 11.0)	7.5 ± 1.4 (4.6 to 10.3)	0.28
Total CT (mm)	14.5 ± 2.4 (9.7 to 21.8)	14.7 ± 2.3 (10.2 to 21.9)	0.29
Cancellous width (mm)	13.4 ± 1.8 (9.3 to 18.8)	13.5 ± 2.0 (9.3 to 19.1)	0.27
Medial CT to bone width (%)	25.3 ± 3.1 (17.3 to 32.7)	25.2 ± 3.1 (17.8 to 33.3)	0.80
Lateral CT to bone width (%)	26.5 ± 4.1 (17.5 to 38.3)	26.5 ± 4.1 (18.6 to 34.7)	0.87
Ratio total CT to bone width (%)	51.8 ± 5.9 (34.9 to 66.1)	51.8 ± 6.1 (37.0 to 66.1)	0.98
Cancellous width (%)	48.1 ± 5.9 (33.9 to 65.2)	48.1 ± 6.2 (33.8 to 63.0)	0.90

CT 5 cm = cortical thickness measured 5 cm below the lesser trochanter; CT 12.5 cm = cortical thickness measured 12.5 cm below the lesser trochanter.
[a]Data are expressed as mean ± SD.
[b]Paired t test.
[c]Location refers to the distance from the lesser trochanter.

Correlation between bone turnover markers and cortical thickness with long-term BP use

No significant correlations were identified between uNTX concentration and the cortical thickness, cortical thickness ratio, and femoral diameter at any level of the femur according to calculated Spearman's rank correlation coefficients (data not shown). There also were no significant correlations between serum PINP concentration and the cortical thickness, cortical thickness ratio, and femoral diameter at any level of the femur according to calculated Spearman's rank correlation coefficients (data not shown).

Discussion

In this study, we evaluated the long-term effects of BP use on femoral cortical thickness and compared the changes in cortical thickness between patients who received long-term BP treatment and control osteoporosis patients who were not treated with BPs. We observed no significant increase in cortical thickness in either of the two groups. Moreover, cortical thickness remained stable after an additional year of continued BP use. Thus, we did not observe any effects of long-term BP use on femoral cortical thickness.

AFF is the reason for interest in generalized femoral cortical thickness. In the first study describing AFF, Odvina and colleagues[6] identified 5 patients who sustained low-energy ST/FS fractures while receiving long-term alendronate treatment. All patients in their study demonstrated histomorphometric evidence of severely suppressed bone turnover. Subsequently, Lenart and colleagues found that the duration of BP use correlated with the cortical thickness ratio measured from radiographs.[5] It has been postulated that this cortical thickening is the result of long-term BP use, which reduces bone remodeling and increases secondary mineralization of bone.[8,9] However, Giusti and colleagues argued that this may not be a plausible explanation for cortical bone thickening.[17] In their study, they found that 5 of 10 patients with AFFs had never been treated with a BP, and this was also true for 3 of 13 patients in the study by Lenart and colleagues.[5] These studies indicated that cortical thickness does not differ between patients with AFFs who had or had not been treated with BPs and that cortical thickness does not increase over time with BP use, thereby strongly supporting the notion that thickened cortices are not a result of long-term BP use.[17] Overall, the discordant findings

regarding the effects of BP use on femoral cortical thickness emphasize the need for further research to elucidate the effects of BPs on the properties of the femur.

The ASBMR appointed a task force to summarize the current state of knowledge, and this group defined AFF according to five major features and four minor features.[2] Because most of these features relate to postfracture conditions, it is difficult to evaluate these features before the occurrence of an AFF. However, two features, localized periosteal thickening of the lateral cortex (major feature) and generalized increase in cortical thickness of the femoral diaphysis (minor feature), are present before AFF. Given that previous studies focused on small numbers of patients with AFF, it is uncertain whether long-term BP use leads to increased cortical thickness. On the basis of our results in the present study, patients with AFFs might have had abnormal cortical thickness before BP use. Long-term BP use is not an essential associated factor for AFF but is a multiple associated factor for AFF.

In one of several previous studies of cortical thickening in long-term BP users, Beck and colleagues found that the mean cortical thickness ratio at the FS had increased by 1.82% after 24 months of alendronate use, whereas it had decreased by approximately 0.31% with placebo.[18] In contrast, Unnanuntana and colleagues performed bone density scanning and reported that long-term alendronate use did not alter cortical thickness on the basis of comparison with thicknesses in untreated controls.[11] Koeppen and colleagues measured the femoral cortical thickness in 58 patients with AFF and 218 controls[19] and reported no difference in the cortical thickness ratio between patients with AFF and controls. Chen and colleagues measured the proximal femoral cortical thickness in 45 patients receiving long-term BP treatment and 12 controls and found no difference in thickness between long-term BP users and controls.[14]

Our results are consistent with those of the previous studies mentioned above. Even after careful comparisons, we did not observe an increase in the femoral cortical thickness in long-term BP users compared with controls. Because AFF does not likely occur without cortical thickening, Koeppen and colleagues proposed two hypotheses regarding cortical thickness in the context of AFFs.[19] The first hypothesis is that cortical thickening is caused by BPs, and the second hypothesis states that increased cortical thickness is a risk factor for AFF regardless of BP use. In a study by Lo and colleagues, in which 38 of 3078 patients with hip or femur fracture had an AFF,[20] almost all AFF patients (97.4%) had received prior BP therapy, with only one exception (2.6%). Considering the results of our present study together with those of the previous studies mentioned above, we propose that either femoral cortical thickening is caused by BP use in some but not all patients, or increased cortical thickness is a risk factor for AFF regardless of BP use.

Our study has several limitations. The first limitation is related to study design. This study was a matched case-control study, and such studies have several major disadvantages, including selection and information bias, which could not be eliminated by increasing the number in the control arm. A longitudinal study is an important approach to investigate the effects of long-term BP treatment, but a longitudinal study would also have several disadvantages, including longitudinal age-related changes in femoral properties[21] and selection bias. Second, almost all participants enrolled in this study were Japanese. Although the incidence rates of AFFs in the Japanese and white populations are similar,[22] these findings might not be generalizable to other ethnic groups or representative of the population as a whole. Third, we measure cortical thickness at three points on radiographs. In a previous report, to our best knowledge, cortical thickness was measured on radiographs at several regions, such as at 3, 5, and 10 cm below the lesser trochanter.[14,21,23] Because the effect of measuring cortical thickness at different locations has not been validated, we established three measurement points in consideration of previous reports and to increase the validity of our results. Further examination is necessary to verify the results obtained at these measurement locations. Fourth, although the femoral radiographs were obtained using a standardized method, the use of radiographs to accurately measure cortical thickness has not been validated. Because radiographs are two-dimensional projections of a three-dimensional structure, the inner edge of cortical bone cannot be precisely determined. Fifth, our results showed the absence of generalized femoral cortical thickening in long-term BP users, but there is a possibility that idiosyncratic response may occur in certain individuals. Therefore, our results cannot eliminate the possibility of increased cortical thickness resulting from long-term BP use. Sixth, we did not perform the longitudinal study in the control group because almost all control patients underwent osteoporosis treatment after initial evaluation. Thus, it was difficult to obtain follow-up radiographs in the absence of osteoporosis treatment.

In conclusion, our study did not find evidence of cortical thickening at the ST/FS area of the femur with long-term BP use.

Disclosures

All authors state that they have no conflicts of interest.

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Authors' roles: Study design: RN, TK, and AS. Study conduct: RN, TK, AN, and TK. Data collection: RN, TK, and AN. Data interpretation: RN, TK, MH, AM, and AS. Drafting manuscript: RN, MH, AM, and AS. Approving final version of manuscript: RN, TK, AN, MH, AM, TK, and AS. RN takes responsibility for the integrity of the data analysis.

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Prevalence and distribution of intervertebral disc degeneration over the entire spine in a population-based cohort: the Wakayama Spine Study

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SUMMARY

Objectives: The purposes of this study were to investigate the prevalence and distribution of intervertebral disc degeneration (DD) over the entire spine using magnetic resonance imaging (MRI), and to examine the factors and symptoms potentially associated with DD.
Design: This study included 975 participants (324 men, mean age of 67.2 years; 651 women, mean age of 66.0 years) with an age range of 21–97 years in the Wakayama Spine Study. DD on MRI was classified into Pfirrmann's system (grades 4 and 5 indicating DD). We assessed the prevalence of DD at each level in the cervical, thoracic, and lumbar regions and the entire spine, and examined DD-associated factors and symptoms.
Results: The prevalence of DD over the entire spine was 71% in men and 77% in women aged <50 years, and >90% in both men and women aged >50 years. The prevalence of an intervertebral space with DD was highest at C5/6 (men: 51.5%, women: 46%), T6/7 (men: 32.4%, women: 37.7%), and L4/5 (men: 69.1%, women: 75.8%). Age and obesity were associated with the presence of DD in all regions. Low back pain was associated with the presence of DD in the lumbar region.
Conclusion: The current study established the baseline data of DD over the entire spine in a large population of elderly individuals. These data provide the foundation for elucidating the causes and mechanisms of DD.

Introduction

Intervertebral disc degeneration (DD) is thought to be the first step in degenerative spinal changes[1], and is typically followed by the gradual formation of osteophytes, disc narrowing, and spinal stenosis[2,3]. Furthermore, DD is considered to be one of the causes of several symptoms (neck pain or low back pain)[4–7]. Therefore, in terms of developing preventive strategies for spinal disorders, it will be important to obtain fundamental data on DD (prevalence, distribution, associated factors, etc.) in a population-based cohort.

We believe that the analysis of DD over the entire spine would provide more useful data than that of DD in the cervical, thoracic, or lumbar regions, separately. In particular, investigations on the extent of DD in these three regions using whole spine magnetic resonance imaging (MRI) could provide useful data concerning intra-individual factors in the development of DD. Several studies have examined degenerative changes in only cervical and lumbar discs because of the high susceptibility to DD in these regions[8–12]. As well, several previous studies have investigated the aging process of the intervertebral discs in the cervical and lumbar regions using MRI in population-based cohorts[13,14]. However, degenerative changes in the thoracic region and correspondingly over the entire spine are poorly understood, because DD in the thoracic region is considered to be an uncommon problem[15,16]. In particular, the stabilization of the thoracic region by the thoracic cage, which

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reduces the mechanical stress imposed on the intervertebral discs, is believed to reduce the incidence of degenerative diseases in this region[17].

Consistent with the above-mentioned previous studies, a population-based cohort analysis of DD in the different spinal regions using MRI could be used to examine the distribution of DD over the entire spine. However, to our knowledge, no previous studies have performed this type of investigation with a population-based cohort.

From the perspective of discogenic pain, the association between DD and symptoms remains controversial, although several reports have found that DD was a source of low back pain[4,5]. Moreover, reports on the association between the presence of DD in the cervical and thoracic regions and neck pain are rare[6,7]. Further, these studies were not performed with population-based cohorts and did not use whole spine MRI. Thus, no study has assessed neck pain and low back pain within individuals using whole spine MRI. To clarify the points described above, we established a population-based cohort study in which participants underwent whole spine MRI and were examined for symptoms associated with spinal disorders. This is our first report of DD over the entire spine based on a cross-sectional examination of a baseline population.

The aims of this study were to examine (1) the prevalence and distribution of DD over the entire spine using MRI in a population-based cohort, (2) the factors associated with DD (age, gender, and body mass index [BMI]) in the cervical, thoracic, and lumbar regions, and (3) the association between DD and symptoms (neck pain and low back pain).

Methods

Participants

The present study, entitled the Wakayama Spine Study, was performed with a sub-cohort of the second visit of the ROAD (Research on Osteoarthritis/osteoporosis Against Disability) study, which was initiated as a nationwide, prospective study of bone and joint diseases in population-based cohorts; the cohorts were established in three communities with different characteristics (i.e., urban, mountainous, and coastal regions) in Japan. A detailed profile of the ROAD study has already been described elsewhere[18,19]. Here, we briefly summarize the profile of the present study. The second visit of the ROAD study began in 2008 and was completed in 2010. All the participants in the baseline study were invited to participate in the second visit. In addition to the former participants, inhabitants aged 60 years and older in the urban area and those aged 40 years and younger in the mountainous and coastal areas who were willing to participate in the ROAD survey were also included in the second visit (both the mountainous and coastal areas were in Wakayama prefecture). Finally, 2674 individuals (900 men, 1774 women) participated in the second visit of the ROAD study, and comprised 1067 individuals (353 men, 714 women) in the urban area, 742 individuals (265 men, 477 women) in the mountainous area, and 865 individuals (282 men, 583 women) in the coastal area. Among these three communities in the ROAD study, the mountainous and coastal areas from which we invited all 1607 participants (547 men, 1060 women) to the Wakayama Spine Study are located in Wakayama prefecture. Of the 1607 participants, a total of 1011 individuals provided written informed consent and attended the Wakayama Spine Study with MRI examinations[20,21]. Among the 1011 participants, those who had MRI-sensitive implanted devices (e.g., pacemakers) and other disqualifiers were excluded. Consequently, 980 individuals underwent MRI of the whole spine. Furthermore, one participant who had undergone a previous cervical operation and four participants who had undergone a previous posterior lumbar fusion were excluded from the analysis. Finally, whole spine MRI results were available for 975 participants (324 men, 651 women) with an age range of 21–97 years (mean, 67.2 years for men and 66.0 years for women). Table I shows the demographic and baseline characteristics of the 975 participants in the present study.

For the purpose of analysis, the participants were divided into five age groups: (1) under 50 years, (2) 50–59 years, (3) 60–69 years, (4) 70–79 years, and (5) 80 years and over. The anthropometric measurements included height, weight, and BMI (weight [kg]/height^2 [m^2]). BMI was categorized according to the guidelines for Asians proposed by the World Health Organization and was thus defined as follows: underweight, less than 18.5; normal, 18.5–23; overweight, 23–27.5; and obesity, greater than 27.5[22]. Experienced orthopedists also asked all participants the following question regarding neck pain and low back pain: "Have you experienced neck pain on most days during the past month, in addition to now?" and "Have you experienced low back pain on most days during the past month, in addition to now?" Those who answered "yes" were defined as having neck pain or low back pain based on previous studies[23–26].

MRI

A mobile MRI unit (Excelart 1.5 T, Toshiba, Tokyo, Japan) was used in the present study, and whole spine MRI was performed for all participants on the same day as the examination. The participants were supine during the MRI, and those with rounded backs used triangular pillows under their head and knees. The imaging protocol included sagittal T2-weighted fast spin echo (FSE) (repetition time [TR]: 4000 ms/echo, echo time [TE]: 120 ms, field of view [FOV]: 300 × 320 mm), and axial T2-weighted FSE (TR: 4000 ms/echo, TE: 120 ms, FOV: 180 × 180 mm).

Sagittal T2-weighted images were used to assess the intervertebral space from C2/3 to L5/S1. C2/3 to C7/T1, T1/2 to T12/L1, and L1/2 to L5/S1 were defined as the cervical region, thoracic region, and lumbar region, respectively. DD grading was performed by an

Table I
Characteristics of participants

	Overall	Men	Women
No. of participants	**975**	**324**	**651**
Age strata (years)			
<50	125	38	87
50–59	175	59	116
60–69	223	65	158
70–79	261	89	172
≧80	191	73	118
Demographic characteristics			
Age, years	66.4 ± 13.5	67.2 ± 13.9	66.0 ± 13.4
Height, cm	156.4 ± 9.4	164.6 ± 7.2	151.5 ± 7.2
Weight, kg	56.8 ± 11.5	64.5 ± 11.6	53.0 ± 9.4
BMI (kg/m^2)	23.3 ± 3.6	23.6 ± 3.4	23.1 ± 3.7
BMI (WHO-Asian category) (*N*)			
Underweight	61	16	45
Normal	425	124	300
Overweight	361	139	221
Obesity	128	44	84
Baseline characteristics			
Symptoms (%)			
Neck pain	24.9	19.4	27.7
Low back pain	43	36.7	42.1
Life style (%)			
Smoking	10.7	25.2	4.1
Alcohol consumption	31.4	56.8	18.8

BMI category for Asian was based on World Health Organization (WHO) guidelines defining underweight (<18.5), normal (18.5–23), overweight (23–27.5), and obese (>27.5). Values are the means ± standard deviation.

orthopedist (MT) who was blind to the background of the subjects. The degree of DD on MRI was classified into five grades based on Pfirrmann's classification system[27], with grades 4 and 5 indicating DD. As shown in Fig. 1, the signal intensity for grade 4 was intermediate to hypointense to the cerebrospinal fluid (dark gray), while the structure is inhomogeneous. Meanwhile, for grade 5, the signal intensity is hypointense to the cerebrospinal fluid (black), and the structure is likewise inhomogeneous. In addition, the disc space is collapsed. It has been reported that loss of signal intensity is significantly associated with the morphological level of the DD and is also associated with both the water and proteoglycan content in a disc[28]. Therefore, we used a grading based on signal intensity and disc height. For evaluating intraobserver variability, 100 randomly selected magnetic resonance images of the entire spine were rescored by the same observer (MT) more than 1 month after the first reading. Furthermore, to evaluate interobserver variability, 100 other magnetic resonance images were scored by two orthopedists (MT and RK) using the same classification. The intraobserver and interobserver variability for DD, as evaluated by kappa analysis, was 0.94 and 0.94, respectively.

"Prevalence of DD", which was defined as "the proportion of the number of participants who had DD at each intervertebral space or region or over the entire spine divided by the total number of participants", was used to describe the frequency of the presence of DD. In the analysis, to clarify the associated factors using multiple logistic regression analysis, we entered a variable of prevalence state (1, presence; 0, absence) of DD as a dependent variable.

Statistical analysis

Multiple logistic regression analysis was used to estimate the association between the presence of DD in each region (cervical, thoracic, and lumbar) as dependent variables and the age group, gender, and BMI category as nominal independent variables after adjustment for the age group, gender and BMI category, mutually.

Additionally, multiple logistic regression analysis was used to estimate the association between the presence of neck pain or low back pain and the presence of DD in each region after adjustment for age, gender, and BMI. Furthermore, in cases in which the presence of DD was significantly associated with a symptom, we examined as a sub-analysis the association between the presence of neck pain or low back pain and the number of DD (categorized into "0", "1 or 2", "3 or more" for ready assessment) in each region using multiple logistic regression analysis after adjustment for age, gender, and BMI. All statistical analyses were performed using JMP version 8 (SAS Institute Japan, Tokyo, Japan).

Results

As shown in Table II, the prevalence of DD in the cervical and thoracic regions and over the entire spine increased with the elevation of the age strata in both men and women. For both genders, the prevalence of DD in the lumbar region was also increased with the elevation of the age strata up to the 70-year-old age group but decreased in the 80-year-old age group. Table III

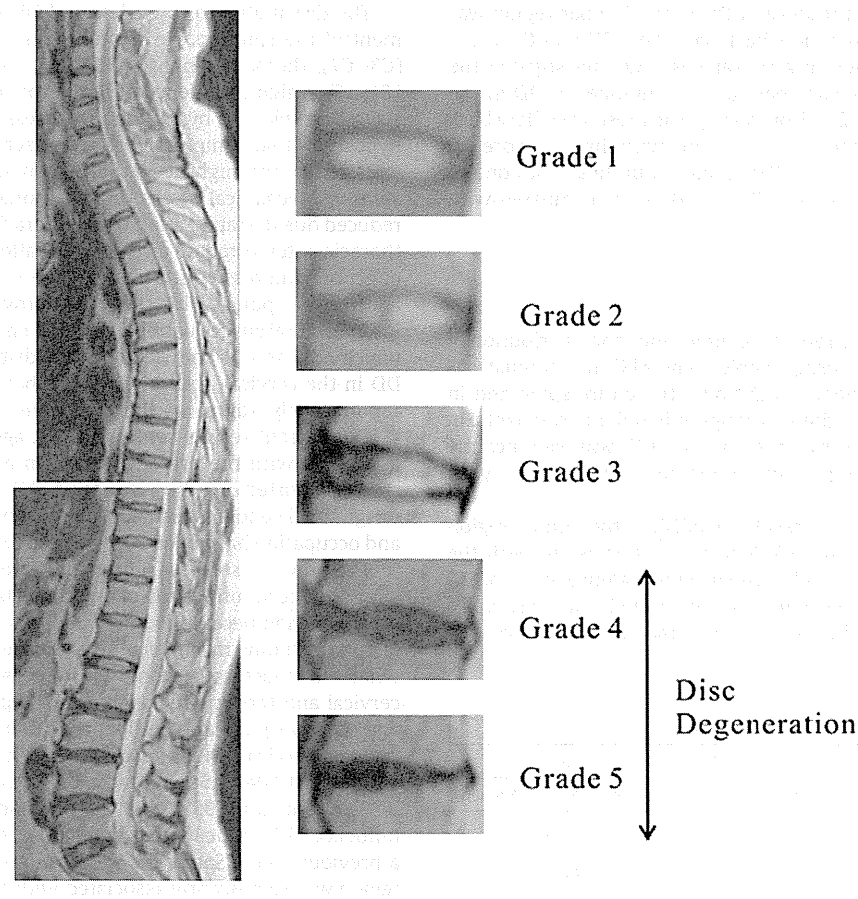

Fig. 1. Mid-sagittal view on T2-weighted images of the whole spine MRI with Pfirrmann classification. The grade is described according to Pfirrmann classification. Grades 4 and 5 were considered degenerated. The signal intensity for grade 4 was intermediate to hypointense to the cerebrospinal fluid (dark gray), while the structure is inhomogeneous. Meanwhile, for grade 5, the signal intensity is hypointense to the cerebrospinal fluid (black), and the structure is also inhomogeneous. Additionally, the disc space is collapsed.

shows the prevalence of intervertebral spaces with DD over the entire spine for the participants in this study. The three highest prevalence levels of DD in the intervertebral spaces in the cervical, thoracic, and lumbar regions were as follows. The prevalence at C5/6 was 51.5% (95% CI: 46.1–56.3) in men and 46% (95% CI: 42.2–49.9) in women, followed by the prevalence at C6/7 of 43.5% in men and 33.3% in women, and at C4/5 of 38.6% in men and 35.8% in women. The prevalence at T6/7 was 32.4% (95% CI: 27.5–37.6) in men and 37.7% (95% CI: 34.1–41.5) in women, followed by the prevalence at T7/8 of 31.8% in men and 36.2% in women, and at T5/6 of 28.4% in men and 35.9% in women. The prevalence at L4/5 was 69.1% (95% CI: 63.9–73.9) in men and 75.8% (95% CI: 72.3–78.9) in women, followed by that at L5/S1 of 66.7% in men and 70.9% in women, and at L3/4 of 59.3% in men and 61.9% in women.

An older age was significantly associated with the presence of DD in each region. Gender was not significantly associated with the presence of DD in each region, although men demonstrated a tendency for a greater number of DD than women in the cervical region. In addition, overweight status (BMI: 23–27.5) was a significantly associated factor in the cervical and thoracic regions, and obesity (BMI: >27.5) was a significantly associated factor in all regions compared with participants of a normal weight (BMI: 18.5–23) (Table IV).

The participants with DD in the cervical region did not significantly differ in terms of the presence of neck pain (OR 0.88, 95% CI: 0.63–1.22, $P = 0.53$). The presence of DD in the thoracic region was not significantly associated with neck pain (OR 0.84, 95% CI: 0.60–1.19, $P = 0.33$) and low back pain (OR 1.08, 95% CI: 0.80–1.47, $P = 0.60$). However, the presence of DD in the lumbar region was significantly associated with low back pain (OR 1.57, 95% CI: 1.02–2.49, $P < 0.05$). Moreover, in a sub-analysis, we investigated the association between low back pain and the number of DD in the lumbar region ("0", "1 or 2", "3 or more"). The presence of low back pain was significantly higher in participants with three or more DD (OR 1.75, 95% CI: 1.11–2.81, $P < 0.05$), but not in those with one or two DD (OR 1.34, 95% CI: 0.84–2.20, $P = 0.22$), as compared with participants without DD.

Discussion

This study is the first to report the prevalence and distribution of DD over the entire spine using whole spine MRI in a population-based cohort. The prevalence of DD over the entire spine and in each of the three spinal regions was higher in older participants. In addition, we noted that the presence of DD was significantly associated with low back pain in the lumbar region but not with neck pain in the cervical region.

Battié *et al.* reviewed the prevalence of DD in the lumbar region and noted that it ranged from 20% to 83%[29]. Consistent with the observations of this review, other reported prevalence levels of DD in the lumbar region have shown wide variation between samples and have often been quite high because the studies had certain drawbacks, including relatively small sample sizes[1,30], narrow age ranges[5,31], and asymptomatic subjects[32]. However, no previous study has assessed the prevalence of DD over the entire spine using whole spine MRI. We noted that the prevalence of DD over the entire spine exceeded 70% in participants less than 50 years of age and was greater than 90% in participants older than 50 years of age.

Little epidemiological data are available concerning DD in the intervertebral space using MRI assessments in a population-based cohort. Matsumoto *et al.*[4] reported that the prevalence of DD in the cervical region was the highest at C5/6 (86% in men and 89% in women over the age of 60 years). In addition, Hanagai *et al.*[33] and Kanayama *et al.*[34] reported that the prevalence of DD in the lumbar region was the highest at L4/5 (67%; mean age 68.4 years) and L5/S1 (49.5%; mean age 39.7 years), respectively. In the present study, the prevalence of DD was the highest at C5/6 (51.5% in men and 46.0% in women) and L4/5 (69.1% in men and 75.8% in women). The prevalence of cervical DD in the previous study by Matsumoto *et al.*[4] was higher than that in the present study. However, the subjects were recruited from volunteers in the hospital rather than a population; thus, the capacity for strict comparisons are limited. Furthermore, few studies have reported age-related DD in the thoracic region. Matsumoto *et al.* reported that the highest prevalence of DD occurred at T7/8 (30.9%; mean age 48.0 y) followed by T6/7 in the thoracic region; however, all 94 participants in this report were asymptomatic[35]. In the present study, we confirmed a high prevalence of DD at T6/7 in the thoracic region. This finding is supported by results from thoracic MRI investigations demonstrating a high prevalence of DD in asymptomatic individuals.

The distribution of prevalence of DD was similar to the alignment of the spine in the sagittal plane, such as cervical lordosis (C3–C7), thoracic kyphosis (T1–T12), and lumbar lordosis (L1–L5)[36]. The high prevalence of DD in the lumbar region can potentially be explained by mechanical stress. Our results support the hypothesis that compressive stress affected DD, since compressive stresses are the highest in the mid-thoracic region of the entire spine[37]. Mechanical stress on the thoracic intervertebral disc is reduced due to stabilization by the thoracic cage, and therefore, the thoracic intervertebral disc may be affected by the detrimental effect of compressive stress caused by posture on the sagittal balance of the spine[38]. This study also provides the first mapping of intervertebral spaces with DD over the entire spine by MRI analysis, which adds to our knowledge of the distribution of prevalence of DD in the cervical, thoracic, and lumbar regions, which has been reported only fragmentarily in previous reports.

Our current results confirmed that age was a significant factor associated with the presence of DD in all three regions. Previous studies reported that the association of DD to factors such as height, weight, and gender was uncertain; however, age, obesity, smoking, and occupation have been suggested to be DD-associated factors[39–42]. The previous studies focused almost entirely on the lumbar region, and the identification of associated factors may be challenging for this region because it is affected to a greater extent by various factors, including mechanical stress. Moreover, it remains unknown what other factors (beyond age) are associated with DD in the cervical and thoracic regions[6,13]. In the present study, overweight and obesity significantly influenced DD in the cervical and thoracic regions (cervical; OR: overweight 1.38 [95% CI 1.00–1.90], obesity 1.60 [95% CI 1.04–2.51], thoracic; OR: overweight 1.64 [95% CI 1.17–2.29], obesity 3.12 [95% CI 1.91–5.19]), and obesity also significantly influenced DD in the lumbar region (OR: 2.56 [95% CI 1.20–6.14]). In a previous study, Samartzis *et al.* reported that DD in the lumbar region was significantly associated with overweight and obesity[39]. However, DD in the cervical and thoracic region did not demonstrate a significant association with BMI, as reported by Okada *et al.*[6] and Matsumoto *et al.*[35]. Of note, the previous studies were

Table II
Prevalence of DD by age strata in men and women

	Entire spine		Cervical		Thoracic		Lumbar	
	Men	Women	Men	Women	Men	Women	Men	Women
Age strata (years)								
<50	71.0	77.0	26.3	27.9	15.7	11.4	55.2	71.2
50–59	91.5	93.1	47.4	49.1	49.1	35.3	86.4	91.3
60–69	98.4	95.5	66.1	54.4	61.5	63.2	96.9	94.3
70–79	95.8	99.4	80.9	72.0	73.0	79.6	96.6	96.5
≧80	93.2	97.4	86.3	85.5	79.4	88.9	82.1	84.5

Values are percentage.

Table III
Prevalence of intervertebral spaces with DD over the entire spine by age strata in men and women

Age strata (years)	C2/3	C3/4	C4/5	C5/6	C6/7	C7/T1	T1/2	T2/3	T3/4	T4/5	T5/6	T6/7	T7/8	T8/9	T9/10	T10/11	T11/12	T12/L1	L1/2	L2/3	L3/4	L4/5	L5/S1
Men																							
Total	28.3	30.2	38.6	51.5	43.5	26.8	20.3	23.4	22.2	24.0	28.4	32.4	31.8	28.7	31.4	25.0	24.0	17.5	30.0	51.5	59.3	69.1	66.7
<50	10.5	10.5	13.1	15.7	13.1	5.2	5.2	7.8	7.8	5.2	10.5	7.8	5.2	2.6	2.6	2.6	0.0	0.0	2.6	10.5	7.8	34.2	47.3
50–59	6.7	11.8	15.2	37.2	27.1	10.1	8.4	6.7	11.8	11.8	16.9	23.7	27.1	16.9	20.3	16.9	13.5	5.1	15.2	35.5	61.0	74.5	50.8
60–69	35.3	36.9	49.2	50.7	40.0	21.0	20.0	24.6	23.0	27.6	27.6	35.3	32.3	36.9	41.5	23.0	24.6	18.4	40.0	60.0	69.0	76.9	75.3
70–79	35.9	35.9	49.4	64.0	51.6	34.8	24.7	26.9	25.8	30.3	33.7	38.2	41.5	35.9	40.4	37.0	31.4	26.9	39.3	69.6	73.0	79.7	79.7
≧80	39.7	42.4	47.9	67.1	65.7	46.5	32.8	39.7	32.8	32.8	41.0	42.4	36.9	35.6	35.6	30.1	35.6	24.6	39.7	56.1	58.9	63.0	65.7
Women																							
Total	21.9	24.8	35.8	46.0	33.3	13.6	15.2	23.1	29.8	31.7	35.9	37.7	36.2	34.2	32.7	28.7	23.8	20.0	31.7	49.7	61.9	75.8	70.9
<50	2.2	3.4	10.3	20.6	10.3	1.1	0.0	1.1	4.5	0.0	1.1	4.5	3.4	5.7	4.5	4.5	1.1	0.0	4.5	12.6	18.3	49.4	56.3
50–59	11.2	9.4	23.2	36.2	23.2	3.4	6.8	12.0	15.5	15.5	16.3	18.1	19.8	12.9	13.7	10.3	6.9	6.9	15.6	35.6	55.6	73.9	70.4
60–69	13.9	20.8	31.0	43.6	29.1	11.3	13.2	18.3	29.7	32.2	37.9	39.8	31.6	32.2	30.3	19.6	15.8	14.5	25.3	55.0	66.4	85.4	75.9
70–79	33.7	34.8	46.5	53.4	42.4	16.2	22.0	34.3	41.2	44.7	50.0	50.0	47.0	45.9	44.7	42.4	34.3	26.1	44.7	64.5	80.2	86.0	81.9
≧80	40.6	46.6	57.6	66.9	52.5	32.2	27.1	40.6	45.7	51.6	57.6	61.0	66.9	61.8	57.6	56.7	52.9	46.1	57.2	62.3	67.5	69.2	58.9

Values are percentage.

conducted with asymptomatic healthy subjects. Therefore, based on our findings, obesity appears to have some influence on the process of DD over the entire spine.

An association between DD in the lumbar region and low back pain was previously demonstrated in a twin study[43]. Moreover, Okada *et al.*[6] reported an association between neck pain and DD in the cervical region, whereas Arana *et al.*[7] found an association between neck pain and DD in the upper thoracic region. Of interest, no agreement has been reached regarding the most appropriate definition of neck pain and low back pain in population cohorts[7]. Nonetheless, we observed a significant association between the presence of DD in the lumbar region and low back pain.

The present study has several limitations. First, it was a cross-sectional study, and therefore, the transition to DD cannot be clarified. Second, the participants included in the present study may not represent the general population, since they were recruited from only two local areas. To confirm whether the participants of the Wakayama Spine Study are representative of the Japanese population, we compared the anthropometric measurements and frequencies of smoking and alcohol consumption between the general Japanese population and the study participants. No significant differences in BMI were observed (men: 24.0 and 23.7, $P = 0.33$; women: 23.5 and 23.1, $P = 0.07$). Further, the proportion of current smokers and those who consumed alcohol (those who regularly smoked or consumed alcohol more than once per month) in men and the proportion of those who consumed alcohol in women were significantly higher in the general Japanese population than in the study population, whereas there was no significant difference in the proportion of current smokers in women (male smokers, 32.6% and 25.2%, $P = 0.015$; female smokers, 4.9% and 4.1%, $P = 0.50$; men who consumed alcohol, 73.9% and 56.8%, $P < 0.0001$; women who consumed alcohol, 28.1% and 18.8%, $P < 0.0001$). These results suggest the likelihood that in this study, participants had healthier lifestyles than those of the general Japanese population[44]. This "healthy" selection bias should be taken into consideration when generalizing the results obtained from the Wakayama Spine Study. Third, the Pfirrmann classification introduced a comprehensive MRI grading system based on the assessment of structure, the distinction of the nucleus and annulus fibrosis, the signal intensity[28], and the height of the intervertebral discs[27]. However, bony endplate alterations, osteophyte changes, spinal stenosis, and disc protrusion are not covered by the Pfirrmann classification. Therefore, it is necessary to perform investigations that include these morphological changes. Finally, the accurate measurement of obesity, such as abdominal obesity and/or body composition, might reveal that obesity has a stronger association with DD; however, the present study examined only BMI as a measurement of obesity. Thus, we plan to examine the girth of the abdomen and body composition using electrical impedance in the assessment of human body composition (the BIA method) in a future study.

In conclusion, this study is the first one to investigate the prevalence of DD over the entire spine in a large population of individuals to establish baseline data for a prospective longitudinal

Table IV
Multiple logistic regression of the association with presence of DD with age, BMI, and gender

	Cervical	Thoracic	Lumbar
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age group (years)			
<50	1	1	1
50–59 (vs <50)	2.45 (1.5–4.06)**	4.60 (2.53–8.76)***	4.47 (2.44–8.48)***
60–69 (vs <50)	3.62 (2.26–5.91)***	12.0 (6.77–22.7)***	9.95 (5.02–21.3)***
70–79 (vs <50)	7.87 (4.86–12.9)***	24.9 (13.8–47.6)***	15.0 (7.26–34.5)***
≧80 (vs <50)	16.9 (9.68–30.5)***	47.0 (24.5–95.6)***	2.94 (1.71–5.13)**
Men (vs women)	1.20 (0.89–1.64)	0.88 (0.64–1.21)	0.70 (0.45–1.09)
BMI (WHO-Asian category)			
Underweight (vs normal)	0.91 (0.49–1.70)	1.36 (0.71–2.67)	0.81 (0.38–1.84)
Normal	1	1	1
Overweight (vs normal)	1.38 (1.00–1.90)*	1.64 (1.17–2.29)*	1.14 (0.71–1.85)
Obesity (vs normal)	1.60 (1.04–2.51)*	3.12 (1.91–5.19)***	2.56 (1.20–6.14)*

BMI category for Asian was based on World Health Organization (WHO) guidelines defining underweight (<18.5), normal (18.5–23), overweight (23–27.5), and obese (>27.5). OR = odds ratio, CI = confidential interval.
*$P < 0.05$, **$P < 0.001$, ***$P < 0.0001$.

study. The prevalence of intervertebral spaces with DD was the highest at C5/6, T6/7, and L4/5 in the cervical, thoracic, and lumbar regions, respectively. DD in the cervical, thoracic, and lumbar regions was significantly associated with age and obesity. A significant positive association was observed between the presence of DD in the lumbar region and low back pain.

Author contributions

All authors worked collectively to develop the protocols and method described in this paper. MT, NY, SM, HO, YI, KN, NT, and TA were principal investigators responsible for the fieldwork in the Wakayama Spine study. MT and SM performed the statistical analysis. All authors contributed to the analysis and interpretation of results. MT wrote the report. All authors read and approved the final manuscript.

Role of the funding source

The sponsors had no role in study design, data collection, data analysis, data interpretation, or in writing of the report.

Conflict of interest

The authors declare no conflicts of interest.

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Clinical Study

The prevalence of cervical myelopathy among subjects with narrow cervical spinal canal in a population-based magnetic resonance imaging study: the Wakayama Spine Study

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Abstract

BACKGROUND CONTEXT: A narrow cervical spinal canal (CSC) is a well-known risk factor for cervical myelopathy (CM). However, no epidemiologic data of the CSC based on a population-based cohort are available.

PURPOSE: The purpose of the study was to investigate the age-related differences in CSC diameters on plain radiographs and to examine the associated magnetic resonance imaging (MRI) abnormalities including cervical cord compression and increased signal intensity (ISI) as well as the clinical CM with the narrow CSC.

STUDY DESIGN/SETTING: This was a cross-sectional study.

PARTICIPANT SAMPLE: Data were obtained from the baseline survey of the Wakayama Spine Study that was performed from 2008 to 2010 in a western part of Japan. Finally, a total of 959 subjects (319 men and 640 women; mean age, 66.4 years) were included.

OUTCOME MEASURES: The outcome measures included in the study were the CSC diameter at C5 level on plain radiographs, cervical cord compression and ISI on sagittal T2-weighted MRI, and physical signs related to CM (eg, the Hoffmann reflex, hyperreflexia of the patellar tendon, the Babinski reflex, sensory and motor function, and bowel/bladder symptoms).

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METHODS: The age-related differences of CSC diameters in men and women were investigated by descriptive statistics. The prevalence of MRI abnormalities and clinical CM was compared among the groups divided by the CSC diameter (less than 13, 13–15, and 15 mm or more). In addition, a logistic regression analysis was performed to determine the association of the CSC diameter with cervical cord compression/clinical CM after overall adjustment for age, sex, and body mass index.
RESULTS: The CSC diameter was narrower with increasing age in both men and women. The prevalence of cervical cord compression, ISI, and the clinical CM was significantly higher in the narrower CSC group. The prevalence of cervical cord compression, ISI, and CM among subjects with CSC diameter less than 13 mm was 38.0%, 5.4%, and 10.1%, respectively. In the logistic model, the CSC diameter was a significant predictive factor for the clinical CM ($p<.0001$).
CONCLUSIONS: This study firstly confirmed the age-related differences in CSC diameters and the significant association of the narrow CSC diameter with CM in a population-based cohort.

Keywords: Cervical spine; Spinal canal stenosis; Cervical myelopathy; Magnetic resonance imaging; Population-based cohort; Epidemiology

Introduction

In cervical spinal disorders such as cervical myelopathy (CM) and spinal cord injury, developmental cervical spinal canal (CSC) stenosis has been considered as an effective predictor of clinical outcome [1,2]. The spinal cord area should be evaluated after comparing with data obtained from asymptomatic subjects of each age group. Age-dependent data are required because the spinal cord may change with age, just as the cerebrum decreases in size with age in elderly subjects. The spinal canal should also be considered in asymptomatic subjects when treating cervical spinal disorders because patients with a tight spinal canal are more susceptible to spinal cord damage. However, the prevalence of spinal cord disorders and CM among patients with CSC of narrow diameter is not known. To date, few studies have focused on age-related differences in the cervical spinal cord and CSC [3,4]. Recent advances in magnetic resonance imaging (MRI) have made it possible to noninvasively obtain clear images of the cervical spinal cord, thereby making evaluation of traumatic spinal cord injury and cervical cord compression more applicable in routine practice. This study was undertaken to clarify age-related differences in the cervical spinal cord and CSC using magnetic resonance imaging (MRI) to establish the basis for morphometric evaluation of patients with cervical spinal cord disorders. More specifically, the purposes of this study were to investigate age-related changes of the CSC in a population-based cohort in Japan and to examine the associated MRI abnormalities including cervical cord compression and increased signal intensity (ISI) as well as the clinical CM with the narrow CSC diameters.

Participants and methods

Participants

The present study is a part of "The Wakayama Spine Study: a population-based cohort," which was a large-scale population-based MRI study. Because a detailed profile of the Wakayama Spine Study has already been described elsewhere, only a brief summary is provided here [5,6]. The Wakayama Spine Study was conducted between 2008 and 2010 in a mountainous region in Hidakagawa, Wakayama, and a coastal region in Taiji, Wakayama. From inhabitants of the Hidakagawa and Taiji regions, 1,063 potential study subjects were recruited for MRI examinations. Among those 1,063 candidates, 52 declined the examination; therefore, 1,011 inhabitants were registered in the present study. Among those 1,011 participants, individuals with MRI-sensitive implanted devices (such as a pacemaker) and other disqualifiers were excluded. Ultimately, the cervical spine was scanned with MRI in 985 participants. Four participants who had undergone a previous cervical operation were excluded from the analysis, and another four participants whose MRI interpretation was difficult because of poor image quality were also excluded. After these exclusions, the present study had 977 participants. Radiographic evaluation of the cervical spine was also performed in 959 of the subjects. In total, both MRI and radiographic results were available for 959 participants (319 men and 640 women) with an age range of 21 to 97 years (mean, 67.3 years for men and 65.9 years for women). The participants completed an interviewer-administered questionnaire of 400 items that included lifestyle information; and anthropometric and physical performance measurements were taken. All study participants provided informed consent, and the study design was approved by the appropriate ethics review boards.

Anthropometric measurements included height (meter), weight (kilogram), and body mass index (BMI; weight [kilogram]/height^2 [m^2]). Medical information concerning neck pain, sensory disturbances, the Hoffmann reflex, the Babinski reflex, and the deep tendon reflex of the patellar tendon was gathered by an experienced orthopedic surgeon. The Hoffmann reflex was elicited with the hand in a neutral position by flicking the distal phalanx of the middle finger and observing flexion of the distal phalanx of the thumb [7,8].

The Babinski reflex was elicited by firmly sweeping from the lateral part of the sole to the base of the toes with a pointed end of a reflex hammer and observing the hallux extensor response [9,10]. Hyperreflexia of the patellar tendon, a positive Hoffmann reflex, and a positive Babinski reflex were defined as aggravation on both sides. A myelopathic sign was defined as the presence of hyperreflexia of the patellar tendon, Hoffmann reflex, or Babinski reflex.

Measurements of CSC diameter and canal-to-body ratio on radiographs

All subjects also underwent lateral radiography with their neck in the neutral position. They were told by an X-ray technician to look straight ahead in a relaxed position. The radiographic data were scanned and calibrated using the ruler, which was put on the film. The sagittal spinal canal diameter at the C5 level was measured as the shortest distance from the midpoint between the vertebral body's superior and inferior end plates to the spinolaminar line. The canal-to-body ratio (CBR) was obtained by dividing the diameter of the spinal canal by that of the vertebral body to assess the tightness of the spinal canal and also to eliminate the magnification effect of radiographs.

Magnetic resonance imaging

An MRI scan of the cervical spine was obtained for each participant using a 1.5-T Excelart imaging system (Toshiba, Tokyo, Japan). All scans were taken in the supine position, except for participants with a rounded back, who used a triangular pillow under their heads and knees. The imaging protocol included a sagittal T2-weighted fast spin-echo pulse sequence (repetition time: 4,000 ms; echo time: 120 ms; and field of view: 300 × 320 mm) and an axial T2-weighted fast spin-echo pulse sequence (repetition time: 4,000 ms; echo time: 120 ms; and field of view: 180 × 180 mm).

MRI measures

Midsagittal T2-weighted images were assessed by an experienced orthopedic surgeon (Keiji Nagata), who was blinded to participants' clinical status.

Evaluation of cervical cord compression

Cervical cord compression was defined as compression with an anterior and/or a posterior component of the spinal cord [6]. Cervical cord compression was evaluated at each intervertebral level from C2–C3 to C7–T1.

Evaluation of signal intensity of the spinal cord

Increased signal intensity was defined as a high-intensity area in contrast with the adjacent isointensity portion of the spinal cord [11]. The ISI was evaluated in the area from C2 to T1.

Measurement of spinal cord diameter

The spinal cord diameter was measured manually at the midpoint of the C5 vertebral body level using the imaging software OsiriX (http://www.osirix-viewer.com/).

Definition of clinical CM

Myelopathy is defined clinically by the presence of myelopathic signs (eg, the Hoffmann reflex, hyperreflexia of the patellar tendon, and the Babinski reflex), usually accompanied by bilateral sensory deficits or sensory level and bowel/bladder symptoms. Among participants with myelopathic signs, cervical cord compression was the essential condition for diagnosing CM.

Statistical analyses

A comparison of baseline characteristics between sexes was performed using the Student *t* test. Differences in the CSC diameter, vertebral body, spinal cord, and CBR among men and women were determined using the Student *t* test. One-way analysis of variance was used to evaluate the differences in CSC diameter, vertebral body, spinal cord, and CBR among different age groups. The chi-square test was used to assess the presence of ISI among different age groups.

For categorical data, the chi-square test was used to assess the presence of significant differences among different diameters of the CSC. For continuous outcomes, the analysis of variance test was used to assess differences among different diameters of the CSC. In addition, to determine the association of ISI, CSC diameter, and CBR with cervical cord compression and CM, logistic regression analysis was used after overall adjustment for age, sex, and BMI. All statistical tests were performed at a significance level of .05 (two-sided). Data analyses were performed using JMP, version 8 (SAS Institute, Inc, Cary, NC, USA).

Results

Characteristics of the participants

The baseline characteristics of the 977 participants, including data for anthropometric measurements and physical performance, are listed in Table 1. There was no

Table 1
Characteristics of men and women participating in the present study

Characteristic	Men	Women
N	319	640
Age, y	67.3±13.8	65.9±13.3
Height, cm	164.6±7.2**	151.6±7.2
Weight, kg	64.4±11.6**	53.0±9.4
Body mass index, kg/m^2	23.7±3.4*	23.1±3.7
Grip strength, kg	37.9±9.1**	23.9±5.9

Note: Significantly different from women by the Student *t* test (*p<.01; **p<.001).
Values are the mean±standard deviation.

Table 2
Radiographic and MRI measures stratified by gender and age strata

	Radiographic measures		MRI measures	
Age strata	Diameter of cervical spinal canal (mm)	Canal-to-body ratio	Increased signal intensity, N (%)	Diameter of spinal cord (mm)
Men				
Overall	14.8±1.3	0.82±0.12	15 (4.6)	6.9±0.9
<50 y	15.2±1.3	0.86±0.09	2 (5.2)	7.3±0.8
50–59 y	14.8±1.7	0.85±0.13	4 (6.9)	7.1±0.9
60–69 y	14.9±1.2	0.82±0.11	3 (4.5)	6.9±0.7
70–79 y	14.8±1.2	0.82±0.11	2 (2.3)	6.9±0.8
≥80 y	14.4±1.1	0.79±0.12	4 (5.5)	6.6±0.9
Women				
Overall	14.1±1.2	0.92±0.13	11 (1.7)	6.8±0.9
<50 y	14.5±1.3	0.99±0.14	1 (1.1)	6.9±0.9
50–59 y	14.4±1.3	0.96±0.12	1 (0.0)	7.0±0.7
60–69 y	14.1±1.1	0.91±0.12	0 (0)	6.8±0.8
70–79 y	13.9±1.1	0.89±0.12	6 (3.5)	6.8±0.9
≥80 y	13.8±1.0	0.86±0.12	3 (2.5)	6.7±0.9

Note: Otherwise indicated, values are mean±standard deviation for each age strata in men and women.

significant difference in age between sexes. Height, weight, and BMI were significantly higher in men than in women.

Age and sex differences of CSC diameter, CBR, ISI, and spinal cord diameter

Table 2 lists the age-related differences in diameters of the CSC, the CBR on radiograph, ISI, and spinal cord diameter on MRI in men and women among different age groups. The CSC diameter was significantly narrower with age in women ($p<.0001$). In men, the CSC diameter had a tendency to be narrower with age, but it was not significantly different in women. The mean diameter of the CSC was not significantly different between men and women. The diameter of the vertebral body was significantly higher in men and women with increasing age ($p<.0001$). The mean CBR in men and women was 0.82 and 0.92, respectively, and it was significantly higher in women than in men at the C5 vertebral level. The CBR was significantly lower with increasing age in both sexes (men, $p=.0004$; women: $p<.0001$).

The prevalence of ISI in all participants was 2.7% (4.6% in men and 1.7% in women) and was significantly higher in men than in women ($p=.007$). The prevalence of ISI was not significantly different with age between sexes. The diameter of the spinal cord was significantly lower with increasing age in both sexes (men, $p=.0012$; women, $p=.0068$). The mean diameter of the spinal cord was not significantly different between men and women.

Prevalence of MRI measures and CM among different diameters of the CSC

Anthropometric measures such as CSC diameter were found to be significantly different according to age (Table 3). Regarding MRI measures, significant differences between different CSC diameters were found with respect to cervical cord compression ($p<.0001$), ISI ($p<.0001$), and spinal cord diameter ($p<.0001$), except for ISI in women. The prevalence of cervical cord compression, ISI, and CM in subjects with a CSC diameter less than 13 mm was 61.9%, 23.8%, and 4.8% in men, respectively. Meanwhile, the prevalence of cervical cord compression, ISI, and CM among female subjects with a CSC diameter less than 13 mm was 33.3%, 1.9%, and 11.1%, respectively. Multiple logistic regression analysis was performed to estimate the predictive factors for CM in MRI and radiographic measurements after adjustment for age, sex, and BMI (Table 4). As an overall result, ISI, CSC diameter, and CBR were significant predictive factors for CM ($p<.01$). There was a positive association between cervical cord compression and spinal cord diameter, whereas spinal cord diameter itself was not a significant predictive factor for CM.

Discussion

The present study is the first population-based study to clarify the normal value of the diameter of the CSC and its association with cervical cord compression, ISI, and CM in Japanese men and women. We clarified that the CSC diameter was narrower with age in both men and women in the population-based cohort. The prevalence of the clinical CM was significantly higher in the narrower CSC group. Furthermore, in the logistic model, the CSC diameter was a significant predictive factor for clinical CM.

In this study, the CSC and vertebral body diameters were measured using plain radiographs because the posterior longitudinal ligament could not be distinguished from the vertebral body on MRI. There have been several reports on the diameter of the CSC. Porter et al. [12] reported that canal size did not appear to change significantly with biomechanical stress and aging. Meanwhile, Goto et al. [3] and Kato et al. [4] reported that the younger generation (younger than 40 years of age) had a statistically wider CSC. Our result was consistent with the latter reports. Why do younger persons have a wider CSC than elderly persons? There are two possible reasons for the differences in CSC diameter between generations. First, the CSC diameter becomes narrower with aging. A CSC with a small diameter is primarily a developmental and not a degenerative phenomenon. However, Hukuda and Kojima [13] reported that the diameter of the vertebral body was wider in older people compared with younger people. Those morphologic changes of the vertebral component may affect the diameter of the CSC. Second, the changes in Japanese eating habits and physique in the past few decades may have contributed to the changes in the diameter of the CSC. The variation of CSC diameter with different generation may be a limited phenomenon in Japan. However, we believe the results prompt future investigations into the various factors affecting the CSC dimensions, apart from aging.