Table 6 Effect of OPA and mJSW at baseline on worsening of WOMAC physical function scores after 3 years

	Crude regression coefficient[b] (95 % CI)	*P* value	Adjusted regression coefficient[a] (95 % CI)	*P* value	Adjusted regression coefficient[b] (95 % CI)	*P* value	Standardized beta
Overall							
OPA (mm^2)	0.10 (0.05 to 0.14)	<0.0001	0.05 (0.002 to 0.10)	0.0393	0.01 (−0.04 to 0.06)	0.6078	0.01
mJSW (mm)	−1.44 (−1.84 to −1.04)	<0.0001	−1.14 (−1.58 to −0.69)	<0.0001	−1.10 (−1.57 to −0.63)	<0.0001	−0.14
Men							
OPA (mm^2)	0.18 (0.07 to 0.29)	0.0012	0.14 (0.03 to 0.26)	0.012	0.10 (−0.02 to 0.23)	0.1095	0.08
mJSW (mm)	−1.27 (−1.95 to 0.59)	0.0003	−0.93 (−1.65 to −0.21)	0.0113	−0.66 (−1.45 to 0.13)	0.1021	−0.08
Women							
OPA (mm^2)	0.08 (0.03 to 0.13)	0.0024	0.03 (−0.02 to 0.09)	0.2521	–	–	–
mJSW (mm)	−1.58 (−2.10 to −1.05)	<0.0001	−1.25 (−1.82 to −0.68)	<0.0001	–	–	

WOMAC Western Ontario and McMaster Universities Osteoarthritis Index, *CI* confidence interval, *OPA* osteophyte area, *mJSW* minimum joint space width

[a] Adjusted regression coefficients for changes in physical function scores were calculated by multiple regression analysis after adjustment for age, BMI, gender, grip strength, and physical function score at baseline overall and after adjustment for age, BMI, grip strength, and physical function score at baseline in men and women

[b] Adjusted regression coefficients for changes in physical function scores were calculated by multiple regression analysis with age, BMI, gender, grip strength, OPA, mJSW, and physical function score at baseline as overall explanatory variables and with age, BMI, grip strength, OPA, mJSW, and physical function score at baseline as explanatory variables in men

The association of osteophytosis with QOL may be complex. Osteophytes may not have any primary effect themselves but rather serve as markers for factors that strongly affect QOL decline. First, osteophytosis appears to start from activation of periosteal layers, with initial generation of chondrophytes and subsequent calcification to real osteophytes. The process is probably an adaptive reaction of the joint to cope with joint instability, and thus, OPA may indicate the severity of joint instability [34], which might lead to pain and physical functional disability, particularly in men. In addition, it is possible that osteophytosis is strongly associated with patellofemoral disease [35], which is associated with knee pain [36]. This is an area where further research would be useful. Nevertheless, our results indicate that the presence or absence of osteophytosis, rather than joint space narrowing, is an appropriate method to predict QOL decline in men.

The present study revealed gender differences in the associations of osteophytosis and joint space narrowing with pain and physical functional disability. Joint space narrowing was an independent predictor for QOL decline measured by WOMAC pain and physical function scores in women, but not in men. Our previous cross-sectional study also showed that the odds ratio of knee pain for KL grade 3 or 4 knee OA was approximately twice as high in women as in men [4]. Considering the definition of KL grade [19], this finding may indicate that joint space narrowing is more strongly associated with pain in women than men. At the same time, osteophytosis is an independent predictor for QOL decline measured by the WOMAC pain and physical function scores in men, but not in women. As mentioned above, osteophytosis may represent joint instability or patellofemoral disease, which may be more strongly associated with pain and physical function than joint space narrowing due to cartilage loss in men. These findings may be partly explained by the lower muscle mass in women compared with men. Previous reports have shown that muscle mass is also associated with QOL [37, 38]. BMI also has different effect on QOL between men and women. To clarify the effect of muscle strength on the association of OPA, mJSW, and BMI with QOL, we classified subjects according to grip strength and examined the association of OPA, mJSW, and BMI with WOMAC pain score. In both men and women with strong muscle strength, OPA was associated with pain rather than mJSW or BMI, whereas in those with weaker muscle strength, mJSW and BMI were associated with pain rather than OPA. We also examined the association of OPA, mJSW, and BMI with WOMAC physical function score according to grip strength, and results were similar to those for pain. This means that muscle strength, rather than gender itself, may affect differences between men and women in the association of mJSW and OPA with QOL.

There is a limitation in the present study. We did not include other weight-bearing joints that can have OA, such as hip OA, in the analysis, although such disorders may also affect QOL decline. However, the prevalence of KL grade 3 or 4 hip OA is 1.4 and 3.5 % in Japanese men and women [39], respectively, which is much less than the prevalence of KL grade 3 or 4 knee OA (13.5 and 24.6 % in Japanese men and women, respectively) [4]. Thus, it is possible that hip OA would not strongly affect the results of the present study.

In conclusion, the present longitudinal study using a large-scale population from the ROAD study revealed

that osteophytosis is a predictor for QOL decline in men. We also revealed gender differences in the association of osteophytosis and joint space narrowing with QOL decline. Future studies, along with longitudinal surveys in the ROAD study, will help further the understanding of osteophytosis and joint space narrowing mechanisms at the knee and their relationship with QOL.

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ORIGINAL ARTICLE

Serum levels of 25-hydroxyvitamin D and the occurrence of musculoskeletal diseases: a 3-year follow-up to the road study

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Abstract
Summary Assessment of serum 25-hydroxyvitamin D levels in association with the occurrence of musculoskeletal diseases using a population-based cohort study design revealed that serum 25-hydroxyvitamin D levels could predict the occurrence of osteoporosis at the femoral neck within 3 years, but not the occurrence of knee osteoarthritis or lumbar spondylosis.
Introduction The aim of this study is to clarify the association between serum 25-hydroxyvitamin D (25D) levels and occurrence of osteoporosis and osteoarthritis in the general population.
Methods The Research on Osteoarthritis/Osteoporosis Against Disability study, a large-scale population-based cohort study, was performed during 2005–2007. Serum 25D levels were measured in 1,683 participants. Of these, 1,384 individuals (81.9 %) completed a second follow-up survey 3 years later. Osteoporosis was defined according to World Health Organization criteria, in which osteoporosis is diagnosed by T-scores of bone mineral density (BMD) that are 2.5 standard deviations (SD) less than normal BMD. Knee osteoarthritis and lumbar spondylosis were defined as Kellgren–Lawrence grade ≥2, using paired X-ray films. Cumulative incidences were determined according to changes in measurements using World Health Organization criteria for osteoporosis or Kellgren–Lawrence grades for osteoarthritis between the baseline and second survey.
Results The mean (SD) serum 25D level of the 1,384 participants in both surveys was 23.4 ng/mL (6.5). The annual cumulative incidences of osteoporosis at L2–4 and the femoral neck were 0.76 and 1.83 %/year, respectively. The incidences of knee osteoarthritis and lumbar spondylosis were 3.3 and 11.4 %/year, respectively. After adjusting for potential associated factors, logistic regression analyses revealed that the odds ratio for the occurrence of femoral neck osteoporosis significantly decreased as serum 25D levels increased (+1 SD; odds ratio 0.67; 95 % confidence interval 0.49–0.92; $p=0.014$).
Conclusions Higher serum 25D levels may prevent the occurrence of osteoporosis at the femoral neck, but not knee osteoarthritis, lumbar spondylosis, or osteoporosis at L2–4.

Keywords 25-Hydroxyvitamin D · Epidemiology · Incidence · Osteoarthritis · Osteoporosis · Population-based cohort study

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Introduction

As the average age of the human population is rapidly increasing, the development of methods to prevent musculoskeletal disorders that impair activities of daily life (ADLs)

and quality of life (QOL) in the elderly has become an urgent need. Osteoporosis and osteoarthritis are major bone and joint health problems that cause impairment of ADL and QOL among the elderly and lead to increased morbidity and mortality in this population. The recent National Livelihood Survey performed by the Ministry of Health, Labour and Welfare in Japan [1] found that arthritis is ranked fourth, and falls and osteoporotic fractures are fifth among the diseases that cause disabilities requiring support and long-term care. Therefore, developing approaches to prevent osteoporosis and osteoarthritis could reduce the impairment of ADL and QOL and subsequent disabilities among the elderly.

Vitamin D influences bone quality and is important in maintaining bone density [2, 3]. A number of studies have reported an association between inadequate vitamin D intake and osteoporosis [4–7]. In contrast, no clear association has been found between vitamin D and osteoarthritis. An association between low levels of 25-hydroxyvitamin D (25D) and prevalent hip osteoarthritis was observed in cross-sectional studies [8, 9]. In addition, it has been shown that low serum 25D levels increased the risk of knee osteoarthritis progression [10] and incident hip joint space narrowing [11]. However, it has also been reported that serum 25D levels did not predict joint space narrowing or loss of cartilage volume of the knee [12] or clinically diagnosed knee or hip osteoarthritis [13].

In the present study, we performed a population-based cohort survey using the Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study cohorts. The second ROAD survey, a 3-year follow-up survey that repeated the baseline examinations performed in the original ROAD study, has been completed. The aim of our study was to determine whether vitamin D inadequacy affects the occurrence of musculoskeletal diseases, including osteoporosis, knee osteoarthritis, and lumbar spondylosis.

Methods

Study participants

The present study was performed using the ROAD study cohorts established in 2005. The ROAD study is a national, prospective study of osteoarthritis that is made up of population-based cohorts from several communities in Japan. Details of the cohort profile have been reported elsewhere [14, 15]. In brief, between 2005 and 2007, a baseline database was created that included clinical and genetic information for 3,040 residents (1,061 men, 1,979 women; mean age, 70.3 years (SD 11.0), 71.0 years (10.7) in men, 69.9 years (11.2) in women) of Japan. The subjects were recruited from resident registration listings in three communities with different characteristics: 1,350 subjects from an urban region in Itabashi, Tokyo; 864 subjects from a mountainous region in Hidakagawa, Wakayama; and 826 subjects from a coastal region in Taiji, Wakayama. In the present study, we enrolled all 1,690 subjects (596 men, 1,094 women; mean age 65.2 years (12.0), 66.3 years (11.7) in men, 64.7 years (12.1) in women) from the mountainous and coastal regions who participated in the ROAD study. Bone mineral density (BMD) measurements and blood and urinary examinations were performed on the participants from the mountainous region and the coastal region.

The study participants provided written informed consent. The study was conducted with the approval of the ethics committees of the University of Tokyo (no. 1264 and no. 1326) and the University of Wakayama Medical University (no. 373).

Baseline assessment

Interviewer-administered questionnaire

Participants completed an interviewer-administered questionnaire that consisted of questions related to lifestyle, including occupation, smoking habits, alcohol consumption, family history, medical history, physical activity, reproductive history, and health-related QOL.

Dietary assessment

A brief diet history questionnaire (BDHQ) was administered to assess the diet of the participants, and nutrient intakes from the preceding month were determined. The BDHQ is a four-page structured questionnaire that includes questions about the frequency of consumption of 80 principal foods. The serving sizes of the foods are described as normal portions that are the standard weight and volume of servings commonly consumed by the general Japanese population. The BDHQ was modified from a comprehensive, 16-page validated self-administered diet history questionnaire [16]. A total of 141 variables, including dietary energy and nutrient intakes, were calculated using an ad hoc computer algorithm for the BDHQ. Detailed explanations accompanied each questionnaire. Well-trained interviewers clarified any unclear sections of the questionnaire, which was completed by the participants at their leisure.

Anthropometric measurements and medical history

Anthropometric measurements, including height and weight, were measured in all participants. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Handgrip strength was measured using a Toei Light handgrip dynamometer (Toei Light Co., Ltd., Saitama, Japan). Both hands were tested and the larger value used to

determine the maximum muscle strength of the subject. Experienced orthopedic surgeons collected medical information about pain, swelling, and range of motion of the knee.

Blood and urinary examinations

Samples were collected between the end of October and the middle of January from participants in the mountainous and coastal areas. All blood and urine samples were extracted between 09:00 and 15:00. After blood samples were centrifuged, the sera and urine samples were immediately placed on dry ice and transferred to a deep freezer within 24 h. Samples were stored at −80 °C until assayed.

Serum levels of 25D were measured using a radioimmunoassay with a ^{125}I-labeled tracer (DiaSorin, Stillwater, MN, USA) [17]. Intact parathyroid hormone (iPTH) levels were measured using an electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Manheim, Germany). Serum N-terminal propeptide of type I procollagen (PINP), a marker of bone formation, was measured using a radioimmunoassay (Orion Diagnostics, Espoo, Finland). Urinary levels of β-isomerized C-terminal telopeptide cross-links of type I collagen (β-CTX), a marker of bone resorption, were determined using an enzyme-linked immunosorbent assay (Fujirebio, Inc., Tokyo, Japan). Urinary β-CTX values were standardized to urinary creatinine concentrations.

BMD examination

Lumbar spine and proximal femur BMD values were determined using dual-energy X-ray absorptiometry (DXA; Hologic Discovery; Hologic, Waltham, MA, USA)

X-ray examination

Plain radiographs of the lumbar spine in the anteroposterior and lateral views and both knees in the anteroposterior view with weight bearing and foot map positioning were obtained.

Three-year follow-up

Between 2008 and 2010, the 1,690 participants were invited to participate in the 3-year follow-up of the ROAD survey, which repeated the baseline examinations.

Definition of osteoporosis and osteoarthritis

Osteoporosis was defined according to World Health Organization criteria; osteoporosis was diagnosed when BMD T-scores were lower than peak bone mass by 2.5 standard deviations (SD) [18]. The mean (SD) for the L2–4 BMD in young adult men and women, as measured by the Hologic DXA in Japan, is 1.011 g/cm^2 (0.119) [19]. Therefore, osteoporosis of the lumbar spine was defined as an L2–4 BMD <0.714 g/cm^2. The mean (SD) BMDs of the femoral neck in young adult men and women are 0.863 g/cm^2 (0.127) and 0.787 g/cm^2 (0.109), respectively [19]. Therefore, osteoporosis at the femoral neck in men and women was defined as a femoral neck BMD <0.546 and <0.515 g/cm^2, respectively.

Knee and lumbar radiographs were read by a single experienced orthopedist who was blinded to participants' clinical status and were categorized using the Kellgren–Lawrence grading scale [20]: grade 0, normal; grade 1, slight osteophytes; grade 2, definite osteophytes; grade 3, disk space narrowing with large osteophytes; and grade 4, bone sclerosis, disk space narrowing, and large osteophytes. In the present study, a subject with at least one knee and at least one lumbar spine with a Kellgren–Lawrence grade ≥2 was defined as having radiographic knee osteoarthritis and lumbar spondylosis, respectively. When a different grade was assigned to each knee, the participant was classified to the higher grade. To examine intra-observer variability of Kellgren–Lawrence grading, 100 randomly selected radiographs of the knee were scored by the same observer 1 month after the initial reading. To determine inter-observer variability, 100 radiographs were scored by two experienced orthopedic surgeons using the same atlas. The Kellgren–Lawrence grade (0–4) intra- and inter-variabilities were confirmed by kappa analysis to be sufficient for assessment (κ=0.86 and κ=0.80, respectively).

Incidence of osteoporosis and osteoarthritis

Cumulative incidence of osteoporosis and osteoarthritis was determined on the basis of changes in measurements between the baseline and second survey. A new case of osteoporosis was identified if an individual's BMD values at baseline were not indicative of osteoporosis, but at follow-up, BMD T-scores were lower than peak bone mass by 2.5 SD. A new case of radiographic knee osteoarthritis was identified if the Kellgren–Lawrence grade at baseline was <2 for both knees and one or both knees were assigned a grade ≥2 at follow-up. A new case of radiographic lumbar spondylosis was identified if the Kellgren–Lawrence grade at baseline was <2 for all lumbar spines and at least one spine was assigned a grade ≥2 at follow-up.

Statistical analysis

All statistical analyses were performed using STATA statistical software (STATA Corp., College Station, TX, USA). Differences in proportions were compared using the chi-squared test. Differences in continuous variables were tested for significance using analysis of variance for comparisons among multiple groups or Scheffe's least significant difference test for pairs of groups.

Logistic regression analysis was used to test the association between serum levels of 25D and the occurrence of osteoporosis at L2–4, osteoporosis in the femoral neck, knee osteoarthritis, and lumbar spondylosis. In the analysis, we used the occurrence of musculoskeletal diseases, such as osteoporosis, knee osteoarthritis, and lumbar spondylosis, as the objective variable and serum levels of 25D (ng/mL, +1 SD) as an explanatory variable, after adjusting for age (+1 year), sex (0, men; 1, women), BMI (+1 kg/m^2), and regional differences (0, mountainous area; 1, coastal area). In addition, we adjusted for factors associated with serum levels of 25D that were identified previously [21]: month of examination (0, October, November, or December; 1, January), smoking (0, never; 1, current), alcohol consumption (0, never; 1, current), serum levels of iPTH (0, <65 pg/mL; 1, ≥65 pg/mL), and total energy from daily amount of intake (+100 kcal/day) and vitamin D (+10 μg/day), calculated based on the BDHQ questionnaire. Furthermore, we adjusted for potential risk factors, including variables regarding exercise, past history, and pain that showed a significant ($p<0.05$) association with the occurrence of each musculoskeletal disease in the simple linear analysis.

Results

Eligible participants

Of the 1,690 study participants, 25D levels were measured at baseline in 1,683 individuals (595 men, 1,088 women; mean age 65.3 years [12.0], 66.3 years [11.7] in men, 64.7 years [12.1] in women). A total of 1,384 individuals (81.9 %; 466 men, 918 women; mean age 66.8 years [11.8], 67.8 years [11.6] in men, 66.4 years [11.8] in women) completed the second follow-up survey that included BMD measurements and X-ray radiography. A total of 251 individuals (14.9 %; 104 men, 147 women) dropped out of the follow-up study. The reasons for the dropouts were as follows: 40 individuals (27 men, 13 women) died, 97 individuals (32 men, 65 women) were ill, 16 individuals (5 men, 11 women) moved away, 8 individuals (4 men, 4 women) were absent, 51 (24 men, 27 women) declined to participate in the second survey, and 39 (12 men, 27 women) had other reasons for not participating in the second survey, including lack of response to the invitation. In addition, 55 individuals (3.3 %; 26 men, 29 women) participated in the second survey, but not all measurements were obtained.

Annual incidence of musculoskeletal diseases

In order to estimate cumulative incidence of osteoporosis and osteoarthritis, participants who had previously been diagnosed with osteoporosis and osteoarthritis at baseline were excluded from the estimation for the incidence of each musculoskeletal disease. Of the 1,384 participants who completed both the baseline and follow-up surveys, 204 individuals who had been diagnosed with osteoporosis at L2–4 or who had been prescribed medication for the treatment of osteoporosis at baseline were excluded. Thus, cumulative incidence of osteoporosis at L2–4 was estimated using data from 1,179 participants. Similarly, cumulative incidence for osteoporosis of the femoral neck, knee osteoarthritis, and lumbar spondylosis was estimated using data from 1,187; 728; and 530 participants, respectively (Table 1).

In those participants who completed both the baseline and follow-up surveys, the annual cumulative incidence of osteoporosis of the lumbar spine and femoral neck was estimated to be 0.76 and 1.83 %/year, respectively. The annual cumulative incidence of knee osteoarthritis and lumbar spondylosis was estimated as 3.3 and 11.4 %/year, respectively. The age and sex distribution of the incidence for each musculoskeletal disease is shown in Fig. 1.

Baseline characteristics of participants and occurrence of musculoskeletal diseases during 3-year follow-up periods

The measured baseline characteristics of the study participants, including serum levels of 25D; anthropometric measurements; lifestyle factors such as residence, smoking, alcohol consumption, and exercise; and medical history of fractures, hip pain, and knee pain, are shown in Table 1.

Serum 25D values categorized according to the occurrence or non-occurrence of musculoskeletal diseases are shown in Table 1. The mean levels of serum 25D were significantly lower in the subjects with femoral neck osteoporosis than those who did not develop femoral neck osteoporosis ($p=0.0088$). In contrast, serum 25D levels did not differ significantly between the groups with or without the occurrence of osteoporosis at L2–4 ($p=0.16$). Serum 25D levels were higher in subjects with knee osteoarthritis and lumbar spondylosis when compared to those who did not have knee osteoarthritis or lumbar spondylosis, although there were no significant differences (knee osteoarthritis, $p=0.15$; lumbar spondylosis, $p=0.10$).

When the osteoporosis at L2–4 occurrence group was compared to the non-occurrence group, participants in the occurrence group tended to have lower BMI ($p=0.031$), were more likely to be women ($p=0.011$), and did not exercise frequently ($p=0.017$). Serum PINP and urinary β-CTX and CTX-II levels were significantly higher in the osteoporosis at L2–4 group than in the non-occurrence group (PINP, $p=0.0001$; β-CTX, $p=0.004$; CTX-II, $p=0.006$). Serum levels

Table 1 Comparison of baseline characteristics of individuals with occurrence or non-occurrence of musculoskeletal diseases during the 3-year follow-up period

	Population at risk (n=1,179)			Population at risk (n=1,187)			Population at risk (n=728)			Population at risk (n=530)		
	Occurrence (n=27)	Non-occurrence (n=1,152)	p (Occurrence vs non-occurrence)	Occurrence (n=65)	Non-occurrence (n=1,122)	P (Occurrence vs non-occurrence)	Occurrence (n=71)	Non-occurrence (n=657)	P (Occurrence vs non-occurrence	Occurrence (n=182)	Non-occurrence (n=348)	P (Occurrence vs non-occurrence)
Means (standard deviations) of serum levels of 25D (ng/mL)	21.7 (5.3)	23.5 (6.6)	0.1556	21.4 (5.5)	23.6 (5.5)	0.0088**	24.2 (6.5)	23.0 (6.6)	0.1493	23.1 (6.5)	22.1 (6.1)	0.1033
Mean values (standard deviations) of selected characteristics												
Age (year)	66.8 (8.9)	62.4 (11.8)	0.06	70.2 (9.0)	61.9 (11.5)	<0.0001***	67.3 (8.2)	58.2 (11.8)	<0.0001***	63.2 (10.8)	56.8 (12.5)	0.0059**
Height (cm)	151.9 (7.8)	157.0 (8.6)	0.0022**	151.4 (6.7)	157.2 (8.7)	<0.0001***	153.9 (8.6)	158.8 (8.6)	<0.0001***	154.3 (9.2)	155.2 (7.9)	0.26
Weight (kg)	50.6 (7.4)	57.7 (10.3)	0.0004***	49.0 (6.4)	58.1 (10.3)	<0.0001***	56.0 (8.8)	56.8 (11.0)	0.56	54.9 (9.7)	53.6 (9.5)	0.15
BMI (kg/m^2)	22.0 (3.0)	23.4 (3.3)	0.0312*	21.5 (3.2)	23.5 (3.3)	<0.0001***	23.6 (2.9)	22.4 (3.2)	0.0035**	23.0 (3.2)	22.2 (3.3)	0.0107*
Frequency of selected characteristics (%)												
Female sex	85.2	61.0	0.011*	84.6	60.6	<0.001***	74.7	58.6	0.009**	71.4	83.1	0.002**
Residing in a coastal area	48.2	56.4	0.39	52.3	56.4	0.52	70.8	56.3	0.012*	42.3	61.5	<0.001***
Current smoking habit (more than once a month)	3.9	13.7	0.15	5.0	13.8	0.05	7.1	16.9	0.034*	14.4	9.8	0.12
Current alcohol consumption (more than once a month)	40.7	44.3	0.71	20.3	45.0	<0.001***	64.8	52.1	0.041*	61.5	60.7	0.85
Regularly walking outside (less than once a week, including job)	11.5	21.3	0.23	19.7	20.2	0.92	29.0	23.0	0.27	22.9	22.7	0.940
Regularly exercising outdoors (football, tennis, baseball, golf, etc.) after graduation from the last school	0.0	17.6	0.017*	7.7	18.1	0.032*	7.0	19.9	<0.001***	12.6	13.5	0.780
History of osteoporotic fractures (hip, spine [clinical, symptomatic], shoulder, wrist)	7.4	2.9	0.17	2.5	4.6	0.30	7.0	2.0	0.009**	5.0	2.9	0.220
Visited the doctor owing to pain in the hip	0.0	4.5	0.32	4.08	3.83	0.93	5.7	4.3	0.67	2.6	5.3	0.230
Visited the doctor owing to pain in either knee	19.1	22.9	0.68	26.4	22.4	0.50	25.9	11.7	0.002**	25.9	17.9	0.050*
Month of examination (January)	22.2	26.8	0.59	32.3	26.2	0.28	42.3	23.1	<0.001***	43.4	26.7	<0.001***
Mean values (standard deviation) of serum and urinary biochemical markers												
Serum levels of iPTH (pg/mL)	40.6 (14.5)	40.7 (31.5)	0.99	43.4 (14.9)	40.9 (38.3)	0.6	40.8 (18.3)	42.0 (46.6)	0.83	41.5 (28.4)	42.4 (49.3)	0.83
Serum levels of PINP (μg/L)	76.1 (21.9)	56.1 (25.4)	0.0001***	73.5 (28.7)	56.5 (26.1)	<0.0001***	59.0 (26.9)	56.3 (27.2)	0.43	59.0 (27.1)	59.2 (28.2)	0.94
Urinary levels of β-CTX (μg/mmol Cr)	245.1 (90.4)	176.4 (121.9)	0.0037**	269.5 (138.6)	176.9 (124.4)	<0.0001***	199.7 (130.2)	170.8 (113.0)	0.0452*	2,11.9 (157.7)	193.6 (134.7)	0.17

Table 1 (continued)

	Population at risk (n=1,179)			Population at risk (n=1,187)			Population at risk (n=728)			Population at risk (n=530)		
	Occurrence (n=27)	Non-occurrence (n=1,152)	p (Occurrence vs non-occurrence)	Occurrence (n=65)	Non-occurrence (n=1,122)	P (Occurrence vs non-occurrence)	Occurrence (n=71)	Non-occurrence (n=657)	P (Occurrence vs non-occurrence	Occurrence (n=182)	Non-occurrence (n=348)	P (Occurrence vs non-occurrence)
Urinary levels of CTX-II (μg/mmol Cr)	327.4 (568.9)	224.8 (173.3)	0.0060**	248.9 (126.3)	223.1 (193.0)	0.29	237.5 (175.0)	189.3 (135.2)	0.0059**	207.6 (138.4)	193.6 (154.5)	0.31
Means (standard deviations) of daily nutrition intake												
Total energy (kcal/day)	1,778.1 (458.6)	1,980.9 (600.0)	0.08	1,800.2 (535.3)	1,982.5 (597.4)	0.0172*	1,963.6 (631.4)	1,964.9 (595.4)	0.99	1,945.9 (581.3)	1,815.9 (489.3)	0.0069**
Vitamin D (μg/day)	18.8 (9.3)	20.4 (12.5)	0.51	20.7 (11.0)	20.3 (12.5)	0.77	23.9 (12.3)	18.5 (11.7)	0.0003***	19.6 (11.0)	18.0 (11.3)	0.12

N number of subjects, *KL* Kellgren–Lawrence grade, *BMI* body mass index, *25D* 25-hydroxyvitamin D, *iPTH* intact parathyroid hormone, *PINP* procollagen type I N-terminal propeptide, *β-CTX* β-isomerized C-terminal telopeptide cross-links of type I collagen, *CTX-II* C-terminal cross-linked telopeptide type II collagen

*p<0.05; **p<0.01; ***p<0.001

of iPTH were not significantly associated with osteoporosis at L2–4.

When the osteoporosis at the femoral neck occurrence group was compared to the non-occurrence group, the participants who had osteoporosis at the femoral neck tended to be older (p<0.0001), tended to have lower BMI ($p\leq$0.0001), were more likely to be female ($p\leq$0.001), did not consume alcohol regularly (p<0.001), did not exercise regularly (p=0.032), and consumed less calories (p=0.017) than those in the non-occurrence group. Serum PINP and urinary β-CTX levels were significantly higher in the participants with osteoporosis at the femoral neck than in those who did not have osteoporosis at the femoral neck (p<0.0001). Serum levels of iPTH and urinary levels of CTX-II were not significantly associated with osteoporosis at the femoral neck.

When participants in the knee osteoarthritis occurrence group were compared to those who did not have knee osteoarthritis, those with knee osteoarthritis were older, had a higher BMI, were less likely to be female, resided in a coastal area, smoked less, consumed more alcohol, exercised less regularly, were more likely to have a history of osteoporotic fractures, and were more likely to have a history of medical visits because of knee pain. In addition, vitamin D levels were significantly higher in the participants with knee osteoarthritis than those in the non-occurrence group (p=0.0003). Although iPTH and PINP serum levels did not differ between the occurrence and non-occurrence groups, urinary β-CTX and CTX-II levels were significantly higher in the knee osteoarthritis occurrence group than those in the non-occurrence group (β-CTX, p=0.045; CTX-II, p=0.006).

Participants with lumbar spondylosis were older, had a higher BMI, were less likely to be female, and were more likely to have a history of past pain in either knee than the participants in the non-occurrence group. Although iPTH, PINP, β-CTX, and CTX-II levels were not different between those with lumbar spondylosis and those without, total daily energy intake was higher in the lumbar spondylosis group than in the non-occurrence group.

Logistic regression analysis between the occurrence of musculoskeletal disease and serum 25D levels

Logistic regression analysis was performed with the occurrence of musculoskeletal diseases, including osteoporosis, knee osteoarthritis, and lumbar spondylosis, as the objective variable and serum 25D levels (ng/mL, +1 SD) as the explanatory variable, after adjusting for age (+1 year), sex (0, men; 1, women), BMI (+1 kg/m^2), and regional differences (0, mountainous area; 1, coastal area). In addition, adjustments were made for factors previously shown to be associated with serum levels of 25D [20], including month of examination

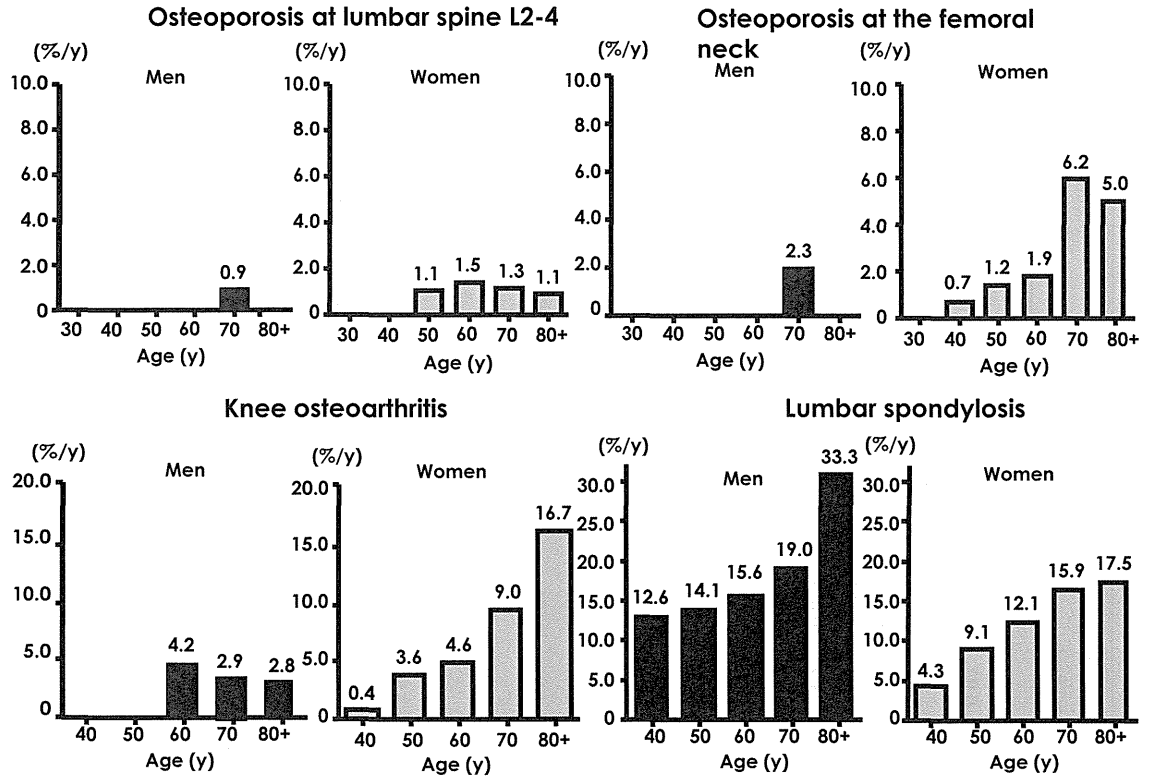

Fig. 1 Cumulative incidence (%/year) of musculoskeletal diseases (osteoporosis at the lumbar spine, osteoporosis at the femoral neck, osteoarthritis of the knee, and lumbar spondylosis) stratified by age and sex

(0, October, November, or December; 1, January), smoking (0, never; 1, current), alcohol consumption (0, never; 1, current), serum iPTH levels (0, <65 pg/mL; 1, ≥65 pg/mL), total daily energy intake (+100 kcal/day), and vitamin D (+10 μg/day) calculated according to responses on the BDHQ questionnaire. Furthermore, we adjusted for potential risk factors that showed a significant ($p<0.05$) association with the occurrence of each musculoskeletal disease in the simple linear analysis described in Table 2. Selected potential factors in each analysis were as follows: osteoporosis at L2–4, regularly exercising outdoors (0, yes; 1, no), serum levels of PINP (+1 SD), and urinary levels of β-CTX (+1 SD) and CTX-II (+1 SD); osteoporosis at femoral neck, regularly exercising outdoors (0, yes; 1, no), and urinary levels of β-CTX (+1 SD) and CTX-II (+1 SD); knee osteoarthritis, regularly exercising outdoors (0, yes; 1, no), history of osteoporotic fractures (0, no; 1, yes), history of knee pain (0, no; 1, yes), and urinary levels of β-CTX (+1 SD) and CTX-II (+1 SD); and lumbar spondylosis, history of knee pain (0, no; 1, yes).

After adjusting for potential risk factors, serum 25D levels were significantly associated with the occurrence of osteoporosis at the femoral neck (odds ratio 0.67; 95 % confidence interval 0.49–0.92; $p=0.014$). However, serum 25D levels were not significantly associated with the occurrence of knee osteoarthritis, lumbar spondylosis, or osteoporosis at L2–4.

Discussion

In the present study, using information from the population-based cohort ROAD study, we estimated the incidence of osteoporosis at L2–4 and at the femoral neck and found that higher serum 25D levels decreased the risk of future occurrence of osteoporosis at the femoral neck, but not the risk of osteoporosis at L2–4 or osteoarthritis, including knee osteoarthritis and lumbar spondylosis.

Previously, we have estimated the age–sex stratified cumulative incidence of knee osteoarthritis and lumbar spondylosis in the Japanese population, using the ROAD study of more than 2,200 subjects who participated at baseline and at the 3-year follow-up study and for whom paired radiographs and complete pain histories were obtained [22, 23]. In contrast, there are few reports estimating the incidence of osteoporosis diagnosed by BMD in the Japanese population [24, 25]. In the present study, we established the population-based cohorts of the ROAD study in identical areas to the previous studies and performed a baseline study between 2005 and 2007 and a follow-up study between 2008 and 2010. Using the data of 1,384 participants from both the baseline and follow-up studies, we estimated the annual cumulative incidence of osteoporosis at the spine L2–4 and at the femoral neck to be 0.76 and 1.83 %/year, respectively. Using the total age and sex

Table 2 Odds ratios of serum 25-hydroxyvitamin D levels influencing the occurrence of musculoskeletal diseases during the 3-year follow-up periods

		Occurrence of osteoporosis at the lumbar spine L2–4			Occurrence of osteoporosis at the femoral neck			Occurrence of knee osteoarthritis			Occurrence of lumbar spondylosis		
Explanatory variables	Reference (at the baseline)	OR	95 % CI	*p*	OR	95 % CI	*p*	OR	95 % CI	*p*	OR	95 % CI	*p*
Serum levels of 25D (ng/mL)	+1 SD	0.87	0.569–1.319	0.504	0.67	0.49–0.92	0.014*	1.23	0.90–1.69	0.198	1.01	0.81–1.28	0.900
Adjusted factors													
Age (year)	+1 year	1.05	1.00–1.09	0.043*	1.11	1.07–1.15	<0.001***	1.10	1.06–1.14	<0.001***	1.04	1.02–1.06	0.001**
Sex	0, men; 1, women	2.74	0.74–10.22	0.132	3.23	1.21–8.61	0.019*	3.24	1.24–8.45	0.016*	0.65	0.34–1.25	0.196
BMI	0, 18.5–27.5 vs 1, <18.5	3.65	0.96–14.34	0.064	8.89	3.33–23.77	<0.001***	1.00[a]	–	–	0.07	0.09–0.51	0.009**
	0, 18.5–27.5 vs 1, >27.5	0.41	0.05–3.17	0.394	0.15	0.02–1.17	0.071	2.29	0.80–6.58	0.125	2.17	1.06–4.45	0.033*
Month of examination	0, October, November, December vs 1, January	0.59	0.20–1.72	0.333	1.59	0.74–3.40	0.234	1.78	0.79–4.02	0.163	1.22	0.70–2.14	0.482
Residing region	0, mountainous area; 1, coastal area	0.71	0.28–1.81	0.467	1.69	0.80–3.58	0.171	1.18	0.53–2.64	0.688	0.71	0.42–1.20	0.197
Smoking	0, ex or never smoker; 1, current smoker	0.47	0.06–3.98	0.491	0.68	0.16–2.84	0.594	1.01	0.27–3.79	0.987	1.28	0.59–2.77	0.529
Alcohol consumption	0, ex or never drinker; 1, current drinker	1.64	0.68–3.94	0.271	0.72	0.34–1.54	0.396	0.83	0.40–1.70	0.604	0.83	0.50–1.37	0.459
Serum levels of iPTH (pg/mL)	0, <65 pg/mL; 1, ≥65 pg/mL	0.39	0.05–3.07	0.371	0.65	0.18–2.41	0.521	1.88	0.65–5.44	0.245	1.88	0.81–4.37	0.145
Total energy from daily food (kcal/day)	+100 kcal	1.00	0.90–1.11	0.991	0.93	0.86–1.01	0.101	1.01	0.94–1.08	0.768	1.04	0.98–1.10	0.179
Vitamin D from daily food (μg/day)	+10 μg	0.84	0.53–1.35	0.479	1.14	0.85–1.54	0.377	1.25	0.94–1.65	0.123	0.94	0.75–1.20	0.636
Selected adjusted factors													
Regularly exercising outdoors	0, yes; 1, no	1.00[a]	–	–	1.15	0.35–3.80	0.819	1.53	0.46–5.03	0.485	–	–	–
History of osteoporotic fractures	0, no; 1, yes	–	–	–	–	–	–	1.95	0.54–7.07	0.311	–	–	–
History of knee pain	0, no; 1, yes	–	–	–	–	–	–	1.84	0.87–3.92	0.111	1.11	0.75–1.20	0.636
Serum levels of PINP (μg/L)	+1 SD	1.51	1.00–2.26	0.040*	1.36	1.01–1.82	0.044*	–	–	–	–	–	–
Urinary levels of β-CTX (μg/mmol Cr)	+1 SD	1.05	0.69–1.61	0.802	1.18	0.91–1.51	0.206	0.76	0.512–1.13	0.176	–	–	–
Urinary levels of CTX-II (μg/mmol Cr)	+1 SD	1.09	0.83–1.44	0.528	–	–	–	1.41	0.96–2.07	0.076	–	–	–

OR odds ratio, *95 %* CI 95 % confidence interval, *25D* 25-hydroxyvitamin D, *BMI* body mass index, *iPTH* intact parathyroid hormone, *PINP* procollagen type I N-terminal propeptide, *β-CTX* β-isomerized C-terminal telopeptide cross-links of type I collagen, *CTX-II* C-terminal cross-linked telopeptide type II collagen

*$p<0.05$; **$p<0.01$; ***$p<0.001$

[a] Omitted from the model

population distributions from the Japanese 2010 census [26], our results indicate that approximately 450,000 people (50,000 men and 400,000 women) aged ≥40 years are affected by osteoporosis at L2–4 and that approximately 1,180,000 people (130,000 men and 1,050,000 women) aged ≥40 years are affected by osteoporosis at the femoral neck.

An association between inadequate vitamin D and osteoporosis has been reported previously. Deficiency of vitamin D results in decreased bone mineralization and secondary hyperparathyroidism and increased cortical bone loss and has been linked to the pathogenesis of osteoporosis and hip fractures [2, 3]. In addition, vitamin D supplementation may help to decrease fractures and falls [27, 28]. In a primary care cohort study of 1,470 postmenopausal Japanese women, there were trends of decreasing incidence of proximal femur and long bone fractures as serum 25D levels increased [29]. However, there are few reports that have assessed the predictive ability of serum 25D levels and the occurrence of osteoporosis itself. In the present study, we confirmed that higher serum 25D levels are associated with the prevention of osteoporosis occurrence, especially at the femoral neck.

There is conflicting information about the association of vitamin D and the occurrence of osteoarthritis. Few longitudinal studies have identified vitamin D deficiency as a risk factor for occurrence or progression of osteoarthritis. Specifically, Lane et al. reported that an increased risk of hip joint space narrowing is associated with low baseline serum 25D levels [11]. McAlindon et al. reported that an increased risk of knee osteoarthritis progression is associated with a low vitamin D intake or low serum 25D levels [10]. Bergink et al. reported that low dietary vitamin D intake increases the risk of progression of radiographic knee osteoarthritis [30]. In addition, cross-sectional studies have shown an association between low 25D levels and prevalent hip osteoarthritis [8, 9]. However, it has also been reported that low serum 25D levels do not increase the incidence of knee osteoarthritis. Felson et al. reported, using data from the Framingham Osteoarthritis Study cohort, that vitamin D status is unrelated to the risk of joint space or cartilage loss in knee osteoarthritis [12]. In addition, Kostari et al. followed a population of 805 subjects who participated in national health examination surveys held in 1978–1980 and 2000–2001 and found no significant association between serum 25D levels and the risk of incident knee or hip osteoarthritis [13]. Our study found no association between serum 25D levels and incident knee osteoarthritis. In addition, although no reports have examined the association between 25D and onset of lumbar spondylosis, we found no association between 25D and incident lumbar spondylosis.

In our previous report examining the association of vitamin D and musculoskeletal diseases at baseline [21], we found that the prevalence of osteoporosis at the L2–4 or at the femoral neck tended to be highest in the vitamin D deficiency group, followed by the vitamin D insufficiency and normal groups, although the groups did not differ significantly. The prevalence of knee osteoarthritis and lumbar spondylosis did not differ between vitamin D levels. In the present follow-up study using the same population, we found that higher levels of serum 25D prevented the occurrence of osteoporosis at the femoral neck, but not knee osteoarthritis or lumbar spondylosis, after adjusting for associated factors. This is the first study to confirm the association between 25D levels and the occurrence of musculoskeletal disorders, using the same population. Therefore, we concluded that the serum 25D levels would be useful in assessing the risk of future osteoporosis, but not the risk of future osteoarthritis.

There are several limitations to this study. First, although the ROAD study includes a large number of participants, these participants may not be representative of the general population. To address this, we compared the anthropometric measurements and smoking frequency and alcohol consumption between the study participants and the general Japanese population. No significant differences were found, with the exception that male ROAD study participants aged 70–74 years were significantly smaller than the overall Japanese population ($p<0.05$) [14]. This difference should be considered when evaluating potential risk factors for men aged 70–74 years. Second, we used Kellgren–Lawrence grade ≥2 as a criterion for the diagnosis of knee osteoarthritis and lumbar spondylosis. The Kellgren–Lawrence scale is a categorical index in which grade 2 is defined as definite osteophytes and grade 3 is defined as disk space narrowing with large osteophytes. Based on this scale, it would be difficult to evaluate osteophytosis and joint space narrowing separately. Thus, all cases of joint space narrowing, with and without the presence of osteophytosis, are categorized into the grade 3. Therefore, to evaluate the severity of knee osteoarthritis using quantitative parameters, a knee osteoarthritis computer-assisted diagnostic system [31] measuring minimum joint space width and area of osteophytosis is under development. In addition, a lumbar spondylosis computer-assisted diagnostic system is also under development. These systems will provide further accuracy in determining the association between the components of osteoarthritis including joint space and osteophytes and serum levels of 25D for early prevention of osteoarthritis. Finally, the measurement of the 25D level in the present study was measured on a single occasion. Thus, we could not exclude the effect of incidental life changes of participants, such as holidays or dietary changes that occurred around the examination date. Owing to budget and lack of manpower, we could not perform recurrent measurements of serum 25D levels to minimize fluctuations in 25D levels due to the effect of environmental factors. However, the large number of participants of the study means that the individual variance in serum 25D levels is diluted.

Importantly, the strength of the present study is that the participation rate in the follow-up survey was very high (81.9 %).

In conclusion, the present study revealed that serum 25D levels could predict the occurrence of osteoporosis at the femoral neck within 3 years, but not the occurrence of knee osteoarthritis or lumbar spondylosis. Raising serum 25D levels may be useful in the prevention of osteoporosis occurrence in the near future.

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Conflicts of interest Noriko Yoshimura, Shigeyuki Muraki, Hiroyuki Oka, Kozo Nakamura, Hiroshi Kawaguchi, Sakae Tanaka, and Toru Akune declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Prevalence of diffuse idiopathic skeletal hyperostosis (DISH) of the whole spine and its association with lumbar spondylosis and knee osteoarthritis: the ROAD study

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Abstract We aimed to assess the prevalence of diffuse idiopathic skeletal hyperostosis (DISH) and its association with lumbar spondylosis (LS) and knee osteoarthritis (KOA) using a population-based cohort study entitled Research on Osteoarthritis/osteoporosis Against Disability (ROAD). In the baseline ROAD study, which was performed between 2005 and 2007, 1,690 participants in mountainous and coastal areas underwent anthropometric measurements and radiographic examinations of the whole spine (cervical, thoracic, and lumbar) and both knees. They also completed an interviewer-administered questionnaire. Presence of DISH was diagnosed according to Resnick criteria, and LS and KOA were defined as Kellgren-Lawrence (KL) grade ≥3. Among the 1,690 participants, whole-spine radiographs of 1,647 individuals (97.5 %; 573 men, 1,074 women; mean age, 65.3 years) were evaluated. Prevalence of DISH was 10.8 % (men 22.0 %, women 4.8 %), and was significantly higher in older participants (presence of DISH 72.3 years, absence of DISH 64.4 years) and mainly distributed at the thoracic spine (88.7 %). Logistic regression analysis revealed that presence of DISH was significantly associated with older age [+1 year, odds ratio (OR): 1.06, 95 % confidence interval (CI): 1.03–1.14], male sex (OR: 5.55, 95 % CI: 3.57–8.63), higher body mass index (+1 kg/m^2, OR: 1.08, 95 % CI: 1.02–1.14), presence of LS (KL2 vs KL0: 1, OR: 5.50, 95 % CI: 2.81–10.8) (KL ≥3 vs KL0: 1, OR: 4.09, 95 % CI: 2.08–8.03), and presence of KOA (KL ≥3 vs KL0: 1, OR: 1.89, 95 % CI: 1.14–3.10) after adjusting for smoking, alcohol consumption, and residential area (mountainous vs coastal). This cross-sectional population-based study clarified the prevalence of DISH in general inhabitants and its significant association with LS and severe KOA.

Keywords Prevalence · Diffuse idiopathic skeletal hyperostosis · Knee osteoarthritis · Lumbar spondylosis · ROAD study

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Introduction

Diffuse idiopathic skeletal hyperostosis (DISH) is characterised by calcification and ossification of soft tissue such as entheses and joint capsules [1]. Resnick and Niwayama specifically defined DISH as the radiographic finding of calcification or ossification along the anterolateral aspects of at least 4 contiguous vertebral levels (across 3 disc spaces), with relative preservation of disc height in the involved vertebral segments and without degenerative disc disease [2]. In 1998, Mata and co-workers [3] developed a

scoring system such that the presence of DISH could be assessed reproducibly. This system scores individuals who fulfill the Resnick criteria by numerically classifying each vertebral level based on the amount of ossification and whether partial or complete bridging of the disc space is present [3].

Although some reports have indicated a significant association between DISH and ossification of the posterior longitudinal ligament (OPLL) [4–7], DISH is thought to be an asymptomatic condition in many affected individuals; however, several clinical symptoms have been described including pain, limited range of spinal motion, and increased susceptibility to unstable spinal fractures after trivial trauma [8]. In addition, dysphagia and airway obstruction at the cervical levels [8, 9], as well as radiculopathy and spinal injury after spinal fracture [10–12], have been reported as clinical manifestations of DISH.

Although the condition is recognised in many parts of the world [13–20], there are relatively few population-based studies concerning its prevalence. Such data are important in order to characterise the burden of the disease. In addition, regarding its characteristics, several epidemiologic studies have reported that DISH is observed mainly in the elderly, and that prevalence increases with age [18, 19]. Men are affected by DISH much more frequently than women [20]. Although metabolic disturbance is hypothesised to be a factor [21, 22], the aetiology of the condition remains unknown.

Based on the definition of DISH as the radiographic finding of calcification or ossification, it appears that the condition might be associated with osteoarthritis (OA) of the spine. The severity of OA, as observed on radiography, was determined according to Kellgren-Lawrence (KL) grading as follows [23]: KL0, normal; KL1, slight osteophytes; KL2, definite osteophytes; KL3, joint or intervertebral space narrowing with large osteophytes; and KL4, bone sclerosis, joint or intervertebral space narrowing, and large osteophytes. KL2 is commonly used as the diagnostic criterion for lumbar spondylosis (LS) or OA at other sites. Thus, LS—defined as KL2 (defined as the definite presence of osteophytes)—could easily be associated with DISH. However, there are few reports to confirm the association between DISH and severe LS with the criterion of KL3 (defined as the presence of intervertebral space narrowing) or KL4 (defined as the presence of bone sclerosis). In addition, there are few reports to clarify the association between DISH and OA at other sites, such as the knees.

We conducted a survey, known as the Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study, using a population-based cohortto determine the prevalence of DISH using lateral whole-spine radiography in recently examined subjects, which included men and women in Japan. Another aim of our study was to clarify the association of DISH with LS and knee osteoarthritis (KOA) based on KL grade.

Materials and methods

Outline of the ROAD study

We conducted the present study using the cohorts established in 2005 for the ROAD study—a nationwide, prospective study of OA comprising population-based cohorts in several communities in Japan. Details of the cohort profile have been reported elsewhere [24, 25]. Briefly, from 2005 to 2007, we developed a baseline database that included clinical and genetic information of 3,040 residents of Japan (1,061 men, 1,979 women) with a mean age of 70.3 (SD, 11) years [men: 71 (SD, 10.7) years, women: 69.9 (SD, 11.2) years]. Subjects were recruited from resident registration listings in three communities with different characteristics: 1,350 subjects (465 men, 885 women) from an urban region in Itabashi, Tokyo; 864 (319 men, 545 women) from a mountainous region in Hidakagawa, Wakayama; and 826 (277 men, 549 women) from a coastal region in Taiji, Wakayama.

Participants completed an interviewer-administered questionnaire of 400 items that included lifestyle information, such as occupation, smoking habits, alcohol consumption, family history, medical history, physical activity, reproductive variables, and health-related quality of life. The questionnaire was prepared by modifying the questionnaire used in the Osteoporotic Fractures in Men Study (MrOS) [26]; some new items also were added to the modified questionnaire. Participants were asked whether they took prescription medication daily or nearly every day (no = 0, yes = 1). If the participants did not know the reason for the prescribed medication, they were asked to bring their medication to the medical doctor (NY).

Anthropometric measurements, including height (cm), body weight (kg), arm span (cm), bilateral grip strength (kg), and body mass index (BMI, kg/m^2) were recorded for each patient. Medical information was recorded by experienced orthopaedic surgeons on systematic, local, and mental status, including information on back, knee, and hip pain; swelling and range of motion of the joints; and patellar and Achilles tendon reflexes.

Eligible subjects of the present study

In the ROAD study, radiographic examination of the thoracic spine was performed only in subjects in mountainous and coastal regions. These subjects also underwent blood and urinary examinations. In the present study, among 1,690 subjects (596 men, 1,094 women) in mountainous and

coastal regions in the ROAD study, we excluded 43 whose radiograph quality was so poor that it was difficult to observe the sites of thoracic–lumbar junction and lumbosacral junction; thus, we analysed 1,647 participants (573 men, 1,074 women) ranging in age from 23 to 94 years (mean: 65.3 years, men: 66.3 years, women: 64.7 years).

Study participants provided written informed consent, and the study was approved by the ethics committees of the University of Wakayama Medical University (No. 373) and the University of Tokyo (No. 1264 and No. 1326).

Radiographic assessment

Plain radiographs of the cervical, thoracic, and lumbar spine in the anteroposterior and lateral views, and bilateral knees in the anteroposterior view with weight-bearing and foot-map positioning were obtained. DISH was diagnosed according to the following criteria, defined by Resnick and Niwayama [2]: (1) flowing ossification along the lateral aspect of at least 4 contiguous vertebral bodies, (2) relative preservation of intervertebral disc height in the involved segments, and (3) absence of epiphyseal joint bony enclosing and sacroiliac joint erosion. In the assessment of lateral radiographs, since it was difficult to read the C7/Th1 to T3/4 vertebral levels, 'whole spine' in the present study implies radiographs assessed from the C0/1 to C6/7, Th4/5 to Th12/L1, and L1/L2 to L5/S1 levels.

The radiographic severity of OA was determined according to the above-mentioned KL grade [20]. Radiographs of each site (i.e., vertebrae and knees) were examined by a single experienced orthopaedic surgeon (SM) who was blinded to the participants' clinical status. In the present study, the maximum grade, diagnosed in at least 1 intervertebral level of the lumbar spine or at least 1 knee joint, was regarded as the subject's KL grade.

Statistical analysis

All statistical analyses were performed using STATA statistical software (STATA Corp., College Station, TX, USA). Differences in proportions were compared using the Chi-square test. Differences in continuous variables were tested for significance using analysis of variance for comparisons among multiple groups or Scheffe's least significant difference test for pairs of groups.

To test the association between the presence of DISH and LS and/or KOA, we used logistic regression analysis. In the analysis, we used presence of DISH as the objective variable (absence = 0, presence = 1), and severity of prevalent LS (KL0, 1 = 0 vs. KL2 = 1; KL0, 1 = 0 vs. KL3 or 4 = 2) and KOA (KL0, 1 = 0 vs. KL2 = 1; KL0, 1 = 0 vs. KL3 or 4 = 2) as explanatory variables, in addition to basic characteristics such as age (+1 year), sex (men = 1, women = 0), BMI (+1 kg/m^2), and regional differences (mountainous area = 0, coastal area = 1). Other potential associated factors were selected with significant or marginal ($p < 0.1$) association with DISH status in a simple linear analysis. The selected explanatory variables for logistic regression analysis are described in the Results section.

Results

Prevalence of DISH was 10.8 % (men: 22.0 %, women: 4.8 %), and was significantly higher in men than in women. Figure 1 shows the prevalence of DISH according to age and sex. Prevalence increased with age in both men and women. Prevalence in subjects classified by age-strata—<50, 50–59, 60–69, 70–79, and ≥80 years—was 1.8, 11.7, 15.4, 32.6, and 39.6 % in men, and 0.7, 1.5, 3.5, 7.6, and 11.8 % in women, respectively.

Table 1 shows the baseline characteristics of the 1,647 participants with and without DISH. In total, subjects with DISH tended to be older, taller, heavier, and have higher BMI than those without DISH ($p < 0.0001$). In the comparison classified by sex, age was significantly higher in those with DISH in both men and women ($p < 0.0001$). In women, mean weight and BMI were significantly higher in those with DISH than in those without DISH (weight: $p < 0.05$, BMI: $p < 0.0001$).

Prevalence of DISH was lower in individuals residing in a coastal area. Individuals with DISH had a higher frequency of smoking and alcohol consumption ($p < 0.05$). The difference in the residing area was significantly observed in men. However, in the comparison classified by sex, differences in smoking and drinking were diluted (Table 1).

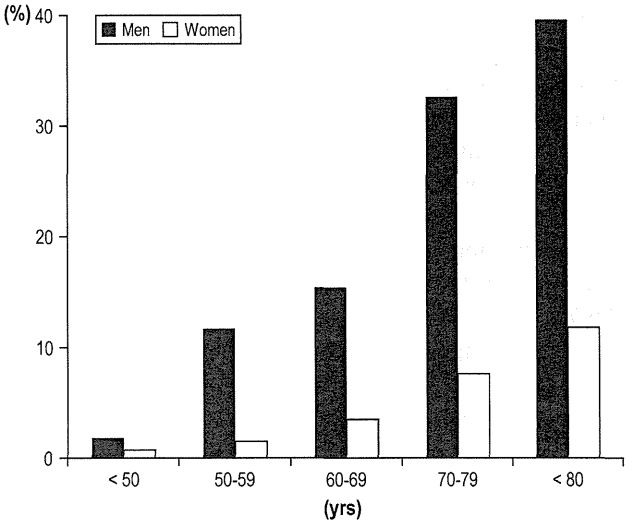

Fig. 1 Prevalence of diffuse idiopathic skeletal hyperostosis (DISH) according to sex and age

Table 1 Mean values (standard deviations) of the anthropometric measurements and the prevalence of lifestyle factors for the participants classified by presence or absence of DISH

	Total (n = 1647)			Men (n = 573)			Women (n = 1074)		
	DISH (−) n = 1470	DISH (+) n = 177	p	DISH (−) n = 447	DISH (+) n = 126	p	DISH (−) n = 1023	DISH (+) n = 51	p
Age (years)	64.4 (12.1)	72.3 (8.4)	<0.0001***	64.6 (12.1)	72.4 (8.2)	<0.0001***	64.3 (12.2)	71.9 (8.8)	<0.0001***
Height (cm)	154.7 (9.2)	158.6 (8.8)	<0.0001***	163.7 (7.3)	162.5 (6.7)	0.0918	150.8 (7.0)	148.9 (5.5)	0.0589
Weight (kg)	55.9 (10.6)	60.1 (10.5)	<0.0001***	62.3 (11.0)	62.1 (10.0)	0.8806	51.9 (8.8)	55.0 (10.3)	0.0126*
BMI (kg/m^2)	22.9 (3.4)	23.8 (3.3)	0.0005***	23.2 (3.2)	23.5 (2.9)	0.3378	22.8 (3.4)	24.7 (3.9)	0.0001***
Residing in the coastal area (%)	50.48	40.11	0.009**	50.3	35.7	0.004**	50.5	51.0	0.951
Current smoking habit (regularly, ≥1 month) (%)	11.9	21.3	<0.001***	29.9	29.0	0.858	3.8	2.0	0.506
Current alcohol consumption (regularly, ≥1 month) (%)	38.7	48.0	0.017*	68.5	61.1	0.122	25.7	15.7	0.108
Presence of LS (KL grade ≥2) (%)	59.1	93.8	<0.001***	72.0	94.4	<0.001***	53.4	92.2	<0.001***
Presence of LS (KL grade ≥3) (%)	35.6	48.0	0.001**	35.4	45.2	0.043*	35.7	54.9	0.005**
Presence of KOA (KL grade ≥2) (%)	48.2	65.5	<0.001***	35.5	58.7	<0.001***	53.8	83.3	<0.001***
Presence of KOA (KL grade ≥3) (%)	18.4	34.5	<0.001***	11.0	27.0	<0.001***	21.7	54.2	<0.001***

DISH diffuse idiopathic skeletal hyperostosis, *BMI* body mass index, *LS* lumbar spondylosis, *KOA* knee osteoarthritis, *KL grade* Kellgren-Lawrence grade

DISH (−) absence of DISH, *DISH (+)* presence of DISH

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 1 also shows the prevalence of LS and KOA defined by KL grade ≥2 and grade ≥3, according to DISH status. In total, the prevalence of LS was higher in those with DISH than in those without DISH ($p = 0.001$). A similar tendency was observed in the prevalence of KOA ($p < 0.001$). This tendency also was noted in the comparison classified by sex.

We classified subjects with DISH into 4 types: (1) cervical, ossification along the lateral aspect of at least 4 contiguous vertebral bodies only in the cervical region (C0/1–C6/7); (2) thoracic, ossification along the lateral aspect of at least 4 contiguous vertebral bodies only in the thoracic region (Th4/5–Th12/L1); (3) lumbar, ossification along the lateral aspect of at least 4 contiguous vertebral bodies only in the lumbar region (L1/2–L5/S1); and (4) diffuse, ossification along the lateral aspect of at least 4 contiguous vertebral bodies in more than 2 regions or through more than 2 regions. Table 2 shows the prevalence of DISH classified by location in the spine. A total of 89 % was shown to be thoracic, whereas the remaining was diffuse; there were no subjects with cervical-type or lumbar-type DISH.

Figure 2 shows the distribution of DISH classified by vertebral level (Th4/5–LS/S1). Among diffuse-type DISH, although 2 subjects had ossification in the cervical region, the cervical site is excluded from the figure. Figure 2 shows that ossification was observed mainly in the middle-lower thoracic sites (Th7/8–Th9/10).

Logistic regression analysis was performed with DISH as the objective variable, LS and KOA as explanatory variables, and patient characteristics including age, sex, BMI, regional differences, smoking, and alcohol consumption as potential risk factors. Presence of DISH was significantly associated with presence of LS (KL2 vs KL0: 1, KL ≥3 vs KL0: 1) and KOA (KL ≥3 vs KL0: 1). Among other potential associated factors, older age, male sex, and higher BMI remained as significantly associated with the presence of DISH (Table 3).

Table 2 Number (proportion, %) of DISH (+) patients classified by spinal ossification site

Type of DISH	Total	Men	Women
Cervical type	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Thoracic type	157 (88.7 %)	111 (88.1 %)	46 (90.2 %)
Lumbar type	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Diffuse type	20 (11.3 %)	15 (11.9 %)	5 (9.8 %)
Total	177 (100.0 %)	126 (100.0 %)	51 (100.0 %)

Cervical type: Ossification along the lateral aspect of at least four contiguous vertebral bodies existing only in the cervical region (C0/1–C6/7)

Thoracic type: Ossification along the lateral aspect of at least four contiguous vertebral bodies existing only in the thoracic region (Th4/5–Th12/L1)

Lumbar type: Ossification along the lateral aspect of at least four contiguous vertebral bodies existing only in the lumbar region (L1/2–L5/S1)

Diffuse type: Ossification along the lateral aspect of at least four contiguous vertebral bodies existing in more than 2 regions or through more than 2 regions

Finally, to clarify the association of DISH with LS and KOA, we performed logistic regression analysis using DISH as an objective variable, LS and KOA as explanatory variables, and patient characteristics including age, sex, BMI, regional differences, smoking, and alcohol consumption as potential risk factors. Presence of DISH was significantly associated with presence of LS (KL2 vs KL0: 1, KL ≥3 vs KL0: 1) and KOA (KL ≥3 vs KL0: 1) independently (Table 4).

Discussion

In the present study, using lateral whole-spine radiographs of recently examined population-based samples, we estimated that the prevalence of DISH was one-tenth of the population, which consisted of participants from the ROAD study. The subjects with DISH tended to be older and had bigger body build than those without DISH. In addition, DISH was observed more frequently in men than

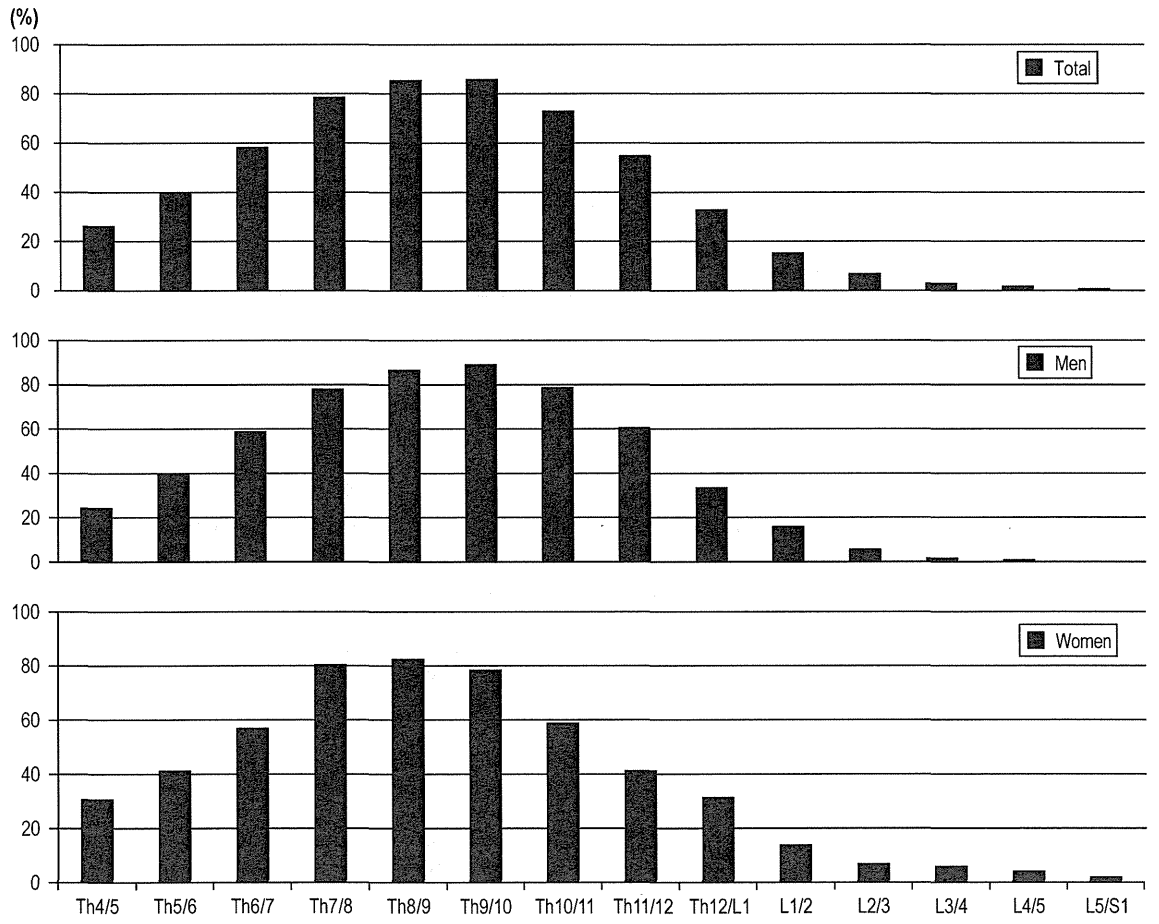

Fig. 2 Prevalence of diffuse idiopathic skeletal hyperostosis (DISH) in each vertebral level, classified by sex

Table 3 Odds ratios of lumbar spondylosis or knee osteoarthritis, and potentially associated factors for the presence of DISH vs. absence of DISH

Explanatory variables	Category	OR	95 % CI	*p*
Lumbar spondylosis				
Presence of LS	0: KL grade = 0, 1, 1: KL grade = 2	5.80	2.97–11.3	<0.001***
	0: KL grade = 0, 1, 2: KL grade ≥3	4.54	2.34–8.84	<0.001***
Age (years)	+1 year	1.07	1.05–1.09	<0.001***
Gender	1: men, 0: women	4.61	3.05–6.99	<0.001***
Region	0: mountainous area, 1: coastal area	0.88	0.61–1.26	0.475
BMI (kg/m^2)	+1 kg/m^2	1.11	1.05–1.17	<0.001***
Smoking	0: ex or never smoker, 1: current smoker	1.65	1.04–2.63	0.034*
Alcohol consumption	0: ex or never drinker, 1: current drinker	0.82	0.56–1.22	0.329
Knee osteoarthritis				
Presence of KOA	0: KL grade = 0, 1, 1: KL grade = 2	1.34	0.85–2.10	0.211
	0: KL grade = 0, 1, 2: KL grade ≥3	2.15	1.32–3.52	0.002**
Age (years)	+1 year	1.07	1.04–1.09	<0.001***
Gender	1: men, 0: women	6.90	4.48–10.6	<0.001***
Region	0: mountainous area, 1: coastal area	0.95	0.65–1.37	0.771
BMI (kg/m^2)	+1 kg/m^2	1.09	1.03–1.15	0.002**
Smoking	0: ex or never smoker, 1: current smoker	1.52	0.95–2.42	0.079
Alcohol consumption	0: ex or never drinker, 1: current drinker	0.85	0.58–1.26	0.431

DISH diffuse idiopathic skeletal hyperostosis, *BMI* body mass index, *LS* lumbar spondylosis, *KOA* knee osteoarthritis, *KL grade* Kellgren-Lawrence grade

OR odds ratios, *95 % CI* 95 % confidence interval

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 4 Odds ratios of lumbar spondylosis and knee osteoarthritis, and potentially associated factors for the presence of DISH vs. absence of DISH

Explanatory variables	Category	OR	95 % CI	*p*
Presence of LS (KL grade = 2)	vs. KL grade = 0, 1	5.50	2.81–10.8	<0.001***
Presence of LS (KL grade ≥3)	vs. KL grade = 0, 1	4.09	2.08–8.03	<0.001***
Presence of KOA (KL grade = 2)	vs. KL grade = 0, 1	1.22	0.77–1.92	0.404
Presence of KOA (KL grade≥ 3)	vs. KL grade = 0, 1	1.89	1.14–3.10	0.013**
Age (years)	+1 year	1.06	1.03–1.14	<0.001***
Gender	1: men, 0: women	5.55	3.57–8.63	<0.001***
Region	0: mountainous area, 1: coastal area	0.88	0.60–1.29	0.522
BMI (kg/m^2)	+1 kg/m^2	1.08	1.02–1.14	0.008**
Smoking	0: ex or never smoker, 1: current smoker	1.59	1.00–2.55	0.052
Alcohol consumption	0: ex or never drinker, 1: current drinker	0.81	0.54–1.21	0.298

DISH diffuse idiopathic skeletal hyperostosis, *BMI* body mass index, *LS* lumbar spondylosis, *KOA* knee osteoarthritis, *KL grade* Kellgren-Lawrence grade

OR odds ratios, *95 % CI* 95 % confidence interval

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

in women, and the most common site was the thoracic vertebrae. Presence of DISH was significantly associated with the presence of KOA and LS, after adjusting for potential associated factors.

There have been several epidemiologic studies on DISH in many parts of the world [12–19]. The results indicate that DISH is observed mainly in men and the elderly; prevalence increases with age, and it is distributed mostly in the thoracic spine. These results are supported by the results of the present study. However, there are considerable differences in the prevalence. Weinfeld et al. [20] reported that genetic or hereditary differences are