

65.5% and 46.6%, that of KL \geq 3 LS was 27.3% and 29.5%, respectively. The incidence of KL \geq 2 was higher in men than women, while, that of KL \geq 3 was similar between men and women, indicating that different mechanisms might influence osteophytosis and disc space narrowing.

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Conflict of Interest

None.

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Prevalence and progression of radiographic ossification of the posterior longitudinal ligament and associated factors in the Japanese population: a 3-year follow-up of the ROAD study

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Abstract

Summary The prevalence of radiographic cervical ossification of the posterior longitudinal ligament (OPLL) in 1,562 Japanese from a population-based cohort was 1.9 %. The presence of OPLL showed a significant association with the femoral neck bone mineral density (BMD), presence of diffuse idiopathic skeletal hyperostosis (DISH) and plasma pentosidine

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levels. Only one new case of radiographic OPLL was detected, but OPLL progressed in all affected subjects.

Introduction The purpose of this study was to clarify the prevalence and progression of radiographic OPLL and the associated factors, using the population-based cohort Research on Osteoarthritis/osteoporosis Against Disability (ROAD).

Methods In the ROAD study, 1,690 participants underwent X-ray examination of the entire spine and both knees. Radiographic OPLL, lumbar spondylosis, knee osteoarthritis and DISH were diagnosed by a single, well-experienced orthopaedic surgeon. An interviewer-administered questionnaire and tests for anthropometric measurements were administered, and the BMDs of the lumbar spine and proximal femur were determined. A new OPLL case was considered if heterotopic ossification in the posterior longitudinal ligament was absent at baseline but present during follow-up. Progression was defined as an increase in the maximum length or width of the ossification at follow-up over that at baseline.

Results Radiographic OPLL was detected in 30 (17 men, 13 women) of 1,562 individuals who underwent X-ray examination of the cervical spine (prevalence=1.9 %). Its prevalence was significantly higher in men than in women ($p=0.007$), but no association with age was observed. In a logistic regression analysis, OPLL showed a significant association with the femoral neck BMD, presence of DISH and plasma pentosidine levels. Only one new case of radiographic OPLL was detected, but OPLL progressed in all affected subjects.

Conclusion This population-based study clarified the prevalence of radiographic OPLL in the Japanese population as well as its progression. OPLL showed significant association with plasma pentosidine levels, BMD and DISH.

Keywords Bone mineral density · Diffuse idiopathic skeletal hyperostosis · Ossification of posterior longitudinal ligament of cervical spine · Plasma pentosidine · Prevalence · Progression

Introduction

Ossification of the posterior longitudinal ligament of the spine (OPLL) is the pathological ectopic ossification of this ligament at the cervical and thoracic spine. It causes myeloradiculopathy as a result of chronic pressure on the spinal cord and nerve roots [1, 2]. Epidemiologic studies have shown a relatively high prevalence of OPLL among the Japanese, a slightly lower prevalence among East Asians and a substantially lower prevalence among whites [3, 4].

In terms of its characteristics, several epidemiological studies have reported that adult-onset obesity and diabetes mellitus (DM) are independent risk factors of OPLL [5, 6]. Further, OPLL often coincides with diffuse idiopathic skeletal hyperostosis (DISH), a systemic disorder of hyperossification. McAfee et al. [7] found that seven (50 %) of 14 patients with OPLL had DISH, and in a Japanese study, DISH was present in 27 (25 %) of 109 patients with OPLL [8].

Besides the coexistence of other disorders such as DM and DISH, little detailed information is available on the profile of OPLL in the general population. These data are important in order to characterise the disease burden. In addition, limited information is available regarding factors associated with OPLL, including biochemical markers of bone turnover, bone mineral density (BMD) values, lifestyle factors, or other coexisting disorders, such as dyslipidaemia, impairment of glucose tolerance, lumbar spondylosis (LS) and knee osteoarthritis (KOA).

Thus, the aims of the present study were to clarify the prevalence of OPLL in the Japanese population and to examine the association of OPLL with biological and environmental factors as well as coexisting disorders. For this, we used a questionnaire survey and the large, population-based cohort Research on Osteoarthritis/osteoporosis Against Disability (ROAD), which included lifestyle factors and nutrition, blood and urinary examinations, BMD measurements and X-ray examinations [9, 10].

Methods

Outline of the ROAD study

We conducted the present study using the cohorts established in 2005 for the ROAD study. The ROAD study is a nationwide, prospective study of OA comprising population-based cohorts from several communities in Japan. The details of the cohort profile have been reported elsewhere [9, 10]. Briefly, in 2005–2007, we created a baseline database that included clinical and genetic information for 3,040 residents of Japan (1,061 men, 1,979 women); the mean age (deviation [SD]) of the participants was 70.3 [11.0] years (71.0 [10.7] years for men and 69.9 [11.2] years for women). The subjects were recruited from resident registration listings in three communities with different characteristics: 1,350 subjects (465 men, 885 women) were

from an urban region in Itabashi, Tokyo; 864 subjects (319 men, 545 women) were from a mountainous region in Hidakagawa, Wakayama and 826 subjects (277 men, 549 women) were from a coastal region in Taiji, Wakayama.

The participants completed an interviewer-administered questionnaire of 400 items that included lifestyle information such as occupation, smoking habits and alcohol consumption; family history; medical history; physical activity; reproductive variables and health-related quality of life. A questionnaire was prepared by modifying the one used in the Osteoporotic Fractures in Men Study [11], and some new items were added to the modified questionnaire. The participants were asked whether they took prescription medication daily or nearly every day (0 = no, 1 = yes). If participants did not know the reason for the prescribed medication, they were asked to bring their medications to the medical doctor (NY).

Anthropometric measurements included height (in centimetres), body weight (in kilograms), arm span (in centimetres), bilateral grip strength (in kilograms) and body mass index (BMI; in kilograms per square metre). Experienced orthopaedic surgeons collected medical information 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.

In 2008–2010, we attempted to locate and follow up all 3,040 subjects. They were invited for the second survey of the ROAD study, which included a 3-year follow-up of the same examinations as the baseline.

Subjects eligible for the present study

In the present study, we enrolled all 1,690 subjects (men, 596; women, 1,094) from mountainous and coastal areas who had enrolled in the ROAD study. In the ROAD study, X-ray examination of the cervical and thoracic spine had been performed only for these subjects and not for those from the urban region. Further, for all these 1,690 participants, the BMDs for the lumbar spine and the proximal femur had been measured using dual energy X-ray absorptiometry (Hologic Discovery; Hologic, Waltham, MA, USA) during the baseline examination. Additionally, blood and urinary examinations had also been performed for these subjects.

The study participants provided written informed consent, and 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).

Radiographic assessment

Plain radiographs were obtained for the cervical, thoracic and lumbar spine in the anteroposterior and lateral views and both knees in the anteroposterior view with weight-bearing and foot-map positioning.

Cervical OPLL was diagnosed using plain radiographs of the cervical spine in the lateral view. OPLL was indicated by the presence of heterotopic ossification in the posterior longitudinal ligament on a lateral cervical radiograph. Radiographic OPLL was diagnosed by a single, experienced orthopaedic surgeon (KN) who was blinded to participants' clinical status. OPLL was classified into the following types: continuous, segmental and mixed. In the original OPLL classification by Tsuyama [3], it was categorised into four modes, namely continuous, segmental, mixed and localised. However, here, because of the small number of subjects in the localised category, these subjects were included in the continuous category. If OPLL was observed, the maximum length (continuous and localised type, upper limit to lower limit; segmental and mixed types, upper limit to lower limit of the longest serial region) and width of ossification were measured using the imaging software OsiriX (<http://www.osirix-viewer.com/>).

In addition, using radiographs of spine and knees, we determined the grade of OA. The severity of radiographic OA was determined according to the Kellgren–Lawrence (KL) grading [12] as follows: 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. Radiographs for each site, i.e. the vertebrae and knees, were examined by a single, experienced orthopaedic surgeon (SM) who was blinded to participants' clinical status. In the present study, the subject's KL grade was considered the maximum grade diagnosed for at least one intervertebral level of the lumbar spine or at least one knee joint.

We also investigated the presence of DISH using whole-spine X-ray films. The criterion for the definite diagnosis of DISH was the presence of four or more vertebral bodies with contiguous ligamentous ossification and calcification, which is known as Resnick and Niwayama's criterion [13]. DISH was diagnosed by a single, experienced orthopaedic surgeon (RK) who was blinded to participants' clinical status.

Blood and urine examinations

Samples were collected from the end of October to the middle of January from both mountainous and coastal areas. All blood and urine samples were extracted between 0900 and 1500 hours. The blood samples were centrifuged, and the sera and urine samples were immediately placed on dry ice and transferred to a deep freezer within 24 h. The samples were stored at -80°C until assayed.

The blood samples were used to measure haemoglobin A1c (HbA1c, Japan Diabetes Society), serum levels of total cholesterol, uric acid and creatinine levels. The analyses were performed at the same laboratory within 24 h of collection (Osaka Kessei Research Laboratories, Inc., Osaka, Japan).

Serum levels of intact parathyroid hormone (iPTH) were measured using an electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). As a marker of bone formation, serum levels of N-terminal propeptide of type I procollagen (PINP) were measured using a radioimmunoassay (Orion Diagnostics, Espoo, Finland). The urinary levels of β -isomerised C-terminal cross-linking telopeptide of type I collagen (β -CTX), a bone resorption marker, were determined using an enzyme-linked immunosorbent assay (Fujirebio, Inc., Tokyo, Japan). Urinary β -CTX values were standardised to urinary creatinine concentrations. Plasma pentosidine levels were detected using a competitive ELISA kit (FSK pentosidine ELISA kit; Fushimi Pharmaceutical, Kagawa, Japan) as previously described [14].

Three-year follow-up and definition of OPLL occurrence and progression

In 2008–2010, the 1,690 subjects were invited to enrol in the second survey of the ROAD study, a 3-year follow-up consisting of examinations identical to those conducted at baseline. Spine and knee radiographs were also obtained at follow-up. All cervical radiographs were read by the same orthopaedic surgeon who read them at the baseline (KN), and he was again blinded to participants' clinical status. He simultaneously compared the X-ray films at the baseline and 3-year follow-up and thereby diagnosed OPLL. A new OPLL case was diagnosed if heterotopic ossification in the posterior longitudinal ligament was absent on the lateral cervical radiograph obtained at baseline but present in that obtained during follow-up. OPLL progression was defined as an increase in the maximum length or width of the heterotopic ossification during follow-up compared to that at baseline.

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 multiple groups or Scheffe's least significant difference test for pairs of groups. All *p* values and 95 % confidence intervals (CI) are two sided.

To test the association between OPLL and potential risk factors, we used logistic regression analysis with the presence or absence of OPLL (0 = absence, 1 = presence) as an objective variable and select potential explanatory variables, in addition to basic characteristics such as age (+1 year), gender (0 = men, 1 = women) and regional differences (0 = mountainous area, 1 = coastal area). The selected associated factors were those that showed a significant ($p < 0.05$) association with OPLL status in a simple linear analysis. To test the association between OPLL progression and associated factors, we used multivariate

regression analysis with the change rate (percent per year) of the maximum length or width as an objective variable and the explanatory variables used in the above-mentioned logistic regression analysis. The explanatory variables in the logistic regression analysis and multivariate regression analysis are described in the “Results” section.

Results

Prevalence of radiographic OPLL

The X-ray radiographs of 1,562 of the 1,690 subjects (92.4 %, 520 men, 1,038 women) showed all parts of the lateral cervical spine, from C1 to C7. Among these 1,562 individuals, 30 (17 men, 13 women) were diagnosed with radiographic OPLL; thus, the prevalence of OPLL was estimated at 1.9 % (men, 3.2 %; women, 1.3 %), and it was significantly higher in men than in women ($p=0.007$).

Figure 1 shows the prevalence of OPLL classified by age and gender. The prevalence of OPLL was not associated with age in either men or women.

In the 30 subjects with radiographic OPLL, the OPLL was categorised into the continuous type in 13 subjects (six men and seven women, 43.3 %), the segmented type in eight (six men and two women, 26.7 %), the mixed type in seven (four men and three women, 23.3 %) and the localised type in two (one man and one woman, 6.7 %). The largest OPLL region was most commonly observed in C4 (ten individuals; 33.3 %; three men and seven women), followed by C5 (nine individuals; 33.0 %; eight men and one woman), C3 (seven individuals; 23.3 %; four men and three women), C6 (three individuals; 10.0 %; two men and one woman) and C2 (one individual; 3.3 %; one woman). The largest OPLL region was not found in C1 or C7 in any subject.

The mean length and width (standard deviation, SD) of the largest region of ossification at the baseline were 27.6 (16.0)

and 3.0 (1.5)mm, respectively. The values in men were 26.1 (14.5) and 2.9 (1.4)mm, and those in women were 29.6 (18.1) and 3.2 (1.5)mm, respectively; thus, no significant difference was observed between men and women in this regard.

Factors associated with OPLL

Table 1 shows the baseline characteristics of 1,562 participants with and without OPLL. Overall, subjects with OPLL tended to be taller and heavier than those without OPLL ($p<0.05$). Further, compared to individuals without OPLL, those with OPLL had higher plasma pentosidine levels and higher BMD values for both the lumbar spine (L2–4) and femoral neck ($p<0.05$).

Table 1 also shows the prevalence of LS, KOA and DISH on the basis of OPLL status. The prevalence of LS with \geq grade 2 KL and that of DISH was higher in the group with OPLL than in the one without OPLL ($p<0.05$), although no significant association was observed between the prevalence of KOA and the presence of OPLL.

Logistic regression analysis was performed with the OPLL status as the objective variable (0 = absence, 1 = presence). As explanatory variables, the analysis involved select associated factors that showed a significant ($p<0.05$) association with OPLL status in the simple linear analysis, namely, height (in centimetres), weight (in kilograms), values of plasma pentosidine (+1 $\mu\text{g/mL}$), BMD of the femoral neck (+1 SD), presence of LS based on KL grade (0 = KL grade 0 or 1, 1 = KL grade ≥ 2) and DISH (0 = absent, 1 = present), after adjustments were made for age (years) and gender (0 = men, 1 = women). As seen from Table 2, plasma pentosidine levels, BMD of the femoral neck and the presence of DISH were found to be significant associated factors for the presence of OPLL (Table 2). Further, when BMD of the lumbar spine (L2–4) was used instead of that of the femoral neck, this factor was also found to be significantly associated with OPLL (+1 SD; odds ratio (OR), 1.52; 95 % CI, 1.05–2.20; $p=0.026$), but the

Fig. 1 Prevalence of OPLL classified by age and gender

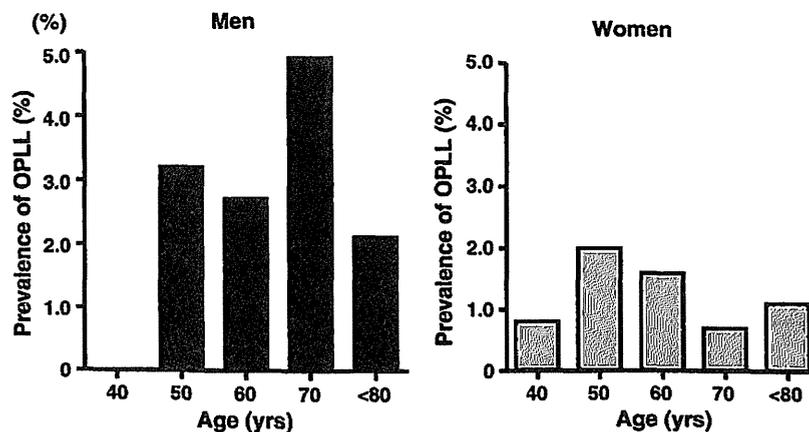


Table 1 Baseline characteristics of participants classified by the presence or absence of OPLL

	Total (N=1,562)			Men (N=524)			Women (N=1,038)		
	OPLL (-) N=1,532	OPLL (+) N=30	<i>p</i>	OPLL (-) N=507	OPLL (+) N=17	<i>p</i>	OPLL (-) N=1,025	N=1,025 N=13	<i>p</i>
Age distribution (prevalence, %)									
30 years and younger	43	0 (0.0)		12	0 (0.0)		31	0 (0.0)	
40–49 years	141	1 (0.7)		39	0 (0.0)		102	1 (1.0)	
50–59 years	291	7 (2.4)	0.729	92	3 (3.2)	0.604	199	4 (2.0)	0.787
60–69 years	449	9 (2.0)		142	4 (2.7)		307	5 (1.6)	
70–79 years	468	11 (2.3)		175	9 (4.9)		293	2 (0.7)	
80 years and older	140	2 (1.4)		47	1 (2.1)		93	1 (1.1)	
Age (years), mean (SD)	62.9 (12.1)	67.0 (9.3)	0.3495	66.0 (11.7)	70.7 (8.0)	0.0990	64.4 (12.2)	62.2 (9.0)	0.5069
Height (cm), mean (SD)	154.9 (9.1)	159.1 (7.5)	0.0132*	163.3 (7.0)	163.9(5.4)	0.7414	150.8 (6.9)	152.8 (4.6)	0.2945
Weight (kg), mean (SD)	55.0 (10.3)	60.3 (10.1)	0.0053**	61.6 (10.5)	62.7 (8.2)	0.6759	51.7 (8.5)	57.1 (11.7)	0.0219*
BMI (kg/m ²), mean (SD)	22.8 (3.2)	23.8 (3.4)	0.1135	23.0 (3.1)	23.3 (2.1)	0.7434	22.7 (3.3)	24.4 (4.6)	0.0671
Residing in the coastal area (%)	49.4	53.3	0.671	46.4	58.8	0.311	50.9	46.2	0.732
Current smoking habit (regularly, ≥1/month) (%)	12.9	23.3	0.095	31.1	41.2	0.377	3.8	0.0	0.472
Current alcohol consumption (regularly, ≥1/month) (%)	39.1	43.3	0.637	66.1	64.7	0.907	25.8	15.4	0.395
Total cholesterol (mg/dL), mean (SD)	208.8 (34.5)	209.6 (36.2)	0.8954	198.6 (34.1)	204.4 (33.5)	0.4874	213.8 (33.6)	216.4 (39.8)	0.7840
Uric acid (mg/dL), mean (SD)	4.84 (1.30)	5.24 (1.21)	0.0943	5.71 (1.26)	5.71 (1.03)	0.9867	4.42 (1.09)	4.65 (1.21)	0.4528
HbA1c (Japan Diabetes Society) (%), mean (SD)	5.17 (0.70)	5.38 (0.79)	0.1124	5.20 (0.79)	5.44 (0.95)	0.2162	5.16 (0.64)	5.29 (0.56)	0.4595
Serum levels of iPTH (pg/mL), mean (SD)	41.2 (34.4)	41.2 (14.2)	0.9952	42.6 (54.4)	41.1 (13.9)	0.9083	40.5 (17.4)	41.3 (15.1)	0.8748
Serum levels of PINP (µg/L), mean (SD)	57.9 (27.0)	52.6 (29.9)	0.2915	47.5 (22.0)	42.6 (14.9)	0.3619	63.1 (27.8)	65.8 (39.2)	0.7301
Urinary levels of β-CTX (µg/mmol Cr), mean (SD)	187.2 (121.3)	150.4 (79.1)	0.0985	128.4 (78.7)	119.8 (58.3)	0.6529	216.2 (128.0)	190.5 (86.8)	0.4693
Plasma levels of pentosidine (µg/mL), mean (SD)	0.058 (0.037)	0.085 (0.140)	0.0005***	0.061 (0.048)	0.102 (0.184)	0.0042**	0.057 (0.030)	0.062 (0.037)	0.5012
BMD of the lumbar spine L2-4 (g/cm ²), mean (SD)	0.925 (0.205)	1.084 (0.205)	<0.0001***	1.038 (0.203)	1.176 (0.176)	0.0058**	0.868 (0.181)	0.965 (0.181)	0.0575
BMD of the femoral neck (g/cm ²), mean (SD)	0.667 (0.137)	0.747 (0.134)	0.0016**	0.739 (0.132)	0.797 (0.110)	0.0727	0.631 (0.124)	0.681 (0.139)	0.1558
Presence of LS (KL grade≥2) (%)	61.8	83.3	0.016*	76.1	100.0	0.022*	54.7	61.5	0.624
Presence of KOA (KL grade≥2) (%)	49.5	56.7	0.440	41.4	41.2	0.986	53.6	76.9	0.093
Presence of DISH (%)	9.4	33.3	<0.001***	0.7	52.9	0.002**	3.8	7.7	0.469

OPLL ossification of posterior longitudinal ligament, SD standard deviation, BMI body mass index, HbA1c haemoglobin A1c, iPTH intact parathyroid hormone, PINP N-terminal propeptide of type I procollagen, β-CTX β-isomerised C-terminal cross-linking telopeptide of type I collagen, BMD bone mineral density, LS lumbar spondylosis, KOA knee osteoarthritis, KL grade Kellgren–Lawrence grade, DISH diffuse idiopathic skeletal hyperostosis, OPLL(-) absence of OPLL, OPLL(+) presence of OPLL

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

Table 2 Odds ratios of potential factors associated with the presence of OPLL vs. the absence of OPLL

Explanatory variables	Reference	OR	95 % CI	<i>p</i>
Age (years)	+1 year	1.03	0.98–1.07	0.269
Gender	0 = men, 1 = women	1.30	0.39–4.34	0.666
Height (cm)	+1 cm	1.04	0.96–1.12	0.352
Weight (kg)	+1 kg	1.00	0.96–1.05	0.909
Pentosidine (µg/mL)	+0.01 µg/mL	1.05	1.00–1.09	0.038*
BMD (femoral neck) (g/cm ²)	+1 SD	1.55	1.04–2.33	0.033*
Presence of LS (KL grade≥2)	0 = no, 1 = yes	1.94	0.67–5.61	0.219
Presence of DISH	0 = no, 1 = yes	2.78	1.11–6.92	0.029*

Logistic regression analysis was performed using the status of OPLL as the objective variable (0 = absence, 1 = presence), and the abovementioned factors were correspondingly adjusted

OPLL ossification of posterior longitudinal ligament, *BMD* bone mineral density, *LS* lumbar spondylosis, *KL grade* Kellgren–Lawrence grade, *DISH* diffuse idiopathic skeletal hyperostosis, *SD* standard deviation, *OR* odds ratios, *95 % CI* 95 % confidence interval

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

association of plasma pentosidine levels and DISH weakened (plasma pentosidine +0.01 µg/mL, 1.04, 0.997–1.087, *p* = 0.069; presence of DISH 2.37, 0.94–6.00, *p* = 0.069).

New occurrence or progression of OPLL

During the three study years, 1,380 individuals (88.3 %; 466 men, 914 women) among the 1,562 subjects at baseline returned for follow-up, and their radiographs were available for observation. Among the 30 individuals with radiographic cervical OPLL at baseline, 25 (83.3 %; 14 men and 11 women) participated in the second survey.

The remaining 1,355 individuals who did not have cervical OPLL at baseline and who participated in the initial and second surveys were regarded as members of the population at risk for the occurrence of OPLL. Among them, only one woman was diagnosed with newly developed radiographic OPLL (incidence 2.46/10,000 per year).

At follow-up, the mean length (in millimetres, SD) and width (in millimetres, SD) of the maximum region of ossification among the 25 individuals with OPLL was 28.7 (16.1) and 3.5 (1.5) mm, respectively. Since the mean values of length and width of the maximum region of ossification of these 25 subjects were 27.0 (16.2) and 3.0 (1.5) mm at the baseline, respectively, both the length and width of the maximum region of ossification increased, although a significant difference was not observed.

To clarify the risk factors associated with this increase in the length and width of the ossification, we performed multivariate regression analysis using the rate of change in these parameters as objective variables and the explanatory variables as those used in the logistic regression analysis, namely height (in centimetres), weight (in kilograms), plasma pentosidine levels (+1 µg/mL), BMD of the femoral neck (+1 SD), presence of LS based on the KL grade (0 = KL grade 0 or 1, 1 = KL grade ≥ 2)

and DISH (0 = absence, 1 = presence). Adjustments for age (years) and gender (0 = men, 1 = women) were made. However, none of the abovementioned variables was found to be significantly associated with the rate of changes in the length or width.

Discussion

In the present population-based study, we clarified the prevalence of radiographic OPLL in the general Japanese population, and we found that it is significantly associated with high plasma pentosidine levels, high BMD and the presence of DISH. The 3-year follow-up study also showed that new cases were very rare, and the length and width of the maximum region of ossification among the subjects with OPLL tended to increase.

The prevalence of OPLL in Japan has been reported to be 1.9 to 4.3 % among individuals aged 30 years and older [1, 15–17]. In other Asian countries, such as in Korea [18, 19] and Taiwan [20], a similar prevalence was reported, but it was lower in Western countries [21], suggesting that ethnic and/or genetic factor(s) could be associated with the onset of OPLL. In the present study, the prevalence of OPLL was found to be 1.9 %. This is consistent with the value found in previous reports. However, it is difficult to clearly distinguish localised-type OPLL from osteophytic changes, and we included two individuals with localised-type OPLL in the OPLL group. Thus, we may have overestimated the presence of radiographic OPLL. If we exclude individuals with localised-type OPLL from the OPLL group, the prevalence of the OPLL in the present study is 1.8 %.

With regard to the gender difference in OPLL prevalence, the prevalence was previously reported to be three times higher in men than in women [22]. We found that men are 2.5 times more likely to have OPLL than women (men 3.2 %, women

1.3 %), which is consistent with results reported previously among Japanese subjects. In contrast, symptomatic OPLL was reported to be usually observed in the sixth decade of life [22], although we were unable to find a significant association between age and the presence of OPLL. This might be explained by the fact that previous studies on the characteristics of OPLL were performed on the subjects with symptomatic OPLL, i.e. they had been clinically diagnosed with OPLL, while our subjects had radiographic OPLL that had not been clinically diagnosed. If the OPLL in our subjects progresses in the future, the peak age at which the symptoms could be expressed may be their 60s.

With regard to the comorbidities of OPLL, several reports have indicated that obesity and DM might be associated with OPLL [5, 6]. In the present study, the values of BMI tended to be higher in the group with OPLL than in that without OPLL, although this difference was not significant. A similar pattern was found in the values of HbA1c, and this finding could be explained by previous findings that the extent of ossification was significantly associated with the fasting serum insulin level but not with the fasting glucose level or the HbA1c level [23]. However, in the ROAD study, since all subjects could not be requested to fast, we could not confirm the association between fasting serum insulin levels and OPLL.

With regard to the association between biochemical markers of bone turnover and OPLL, Matsui et al. showed that the levels of the bone markers serum procollagen type I carboxyl-terminal peptide and intact osteocalcin were higher in patients with OPLL than in normal subjects [24]. This suggested that OPLL was associated with biochemical markers of bone turnover. In the present study, to evaluate the role of bone metabolism in OPLL, we compared the serum levels of iPTH and PINP as bone formation markers and the urinary levels of β -CTX between the groups with and without OPLL. However, we could not find significant differences between the groups.

Instead, the plasma pentosidine levels of the OPLL group were found to be significantly higher than those of the group without OPLL. This tendency remained after potential associated factors were adjusted for. Pentosidine is an advanced glycation end product, products generated by the sequential nonenzymatic glycosylation of protein amino groups [25] that accumulate in various tissues including kidney and coronary arteries, resulting in the development of diabetic vascular complications [26]. The concentrations of pentosidine in cortical and trabecular bone are reported to be adversely associated with bone strength [27–29]. Yamamoto et al. [30] found that serum pentosidine levels were positively associated with the presence of vertebral fractures in postmenopausal women with type 2 diabetes. Renal insufficiency was reported to be a dominant determinant of serum pentosidine levels [31] because of which serum pentosidine levels are increased in patients with chronic renal failure [32, 33]. However, no report has shown the association between pentosidine levels and the

presence of OPLL. On the basis of the abovementioned reports, we performed multivariate logistic regression analysis using the same explanatory factors we had used in the analysis shown in Table 2, along with the estimated glomerular filtration rate. We found that the plasma pentosidine levels were still significantly related to the presence of OPLL (OR, 1.05; 95 % CI, 1.00–1.09; $p=0.042$). We speculate that the levels of pentosidine might be associated with ectopic ossification, such as vascular calcification in patients with renal dysfunction, or the presence of OPLL, directly or indirectly, although the currently available information is inadequate to prove this hypothesis. One reason for the inadequacy of the information obtained in this study could be that we did not evaluate genetic factors in the present study. Further investigations are needed to clarify whether the observed relationship between pentosidine levels and OPLL remains after analysis of other possible confounders, including genetic factors.

In addition to the biochemical markers, high BMDs have been observed in patients with OPLL [24, 34, 35]. However, Morio et al. reported that the BMD was lower in patients with advanced OPLL [36], suggesting that the disuse atrophy may result during advanced-stage OPLL. Our results also showed that subjects with OPLL had higher BMDs. However, the subjects in the present study all had radiographically determined OPLL but few clinical symptoms, so their condition may not have been in the advanced stage. Therefore, based solely on the results of the present study, we were unable to discuss the association between BMD and advanced-stage OPLL.

Several reports have shown that the coexistence of OPLL and DISH is quite common [4, 7, 8]. The pathogenesis of DISH and OPLL has been speculated to be similar, although the details remain unclear. For example, Havelka et al. analysed intron 6 (–4) polymorphisms in the COL 11 A2 gene in Czech patients with DISH and Japanese patients with OPLL, but they found no agreement between the data of subjects with DISH and OPLL [37]. Additional studies with a broader spectrum of genotyping and a larger cohort of patients may clarify the presence or absence of genetic relations between DISH and OPLL.

Few studies have been reported regarding the incidence of OPLL in the general population because OPLL is relatively rare and based on ethnicity, as noted. Using data collected in a pilot study in the corporation of 360 Japanese hospitals [3], Tsuyama described the incidence of OPLL and found that 2,142 patients were treated in these hospitals and the estimated incidence of OPLL was 19 patients per million persons of the total population [3]. In the present study, only one new case of OPLL was detected, so we could not accurately estimate the incidence of OPLL and compare our results to those of previous reports. In order to confirm the incidence of OPLL, we need to follow this cohort for a longer time.

Several studies have investigated the course of OPLL. Chiba et al. use computer-assisted measurement to examine OPLL

progression, and they found that the rate of OPLL progression was 56.5 % over 2 years, and this rate was most common in younger patients with continuous- and mixed-type OPLL [38]. Murakami et al. followed the case of a 67-year-old man who had had cervical OPLL for more than 26 years, and they found that the rate of OPLL progression was 2.2, 8.8 and 2.0 mm/year from 1–4, 4–8 and 8–10 years after the first visit, respectively [39]. However, to our knowledge, no study has reported the progression of radiographically defined OPLL in the general population. In the present study, we found that both the length and width of the maximum region of ossification increased during the 3 years of the study, although it was not a significant change. A previous report [39] found no evidence of OPLL progression after 10 years. We must carefully examine whether or not radiographically defined OPLL progresses to clinical OPLL.

This study has several limitations. First, although the ROAD study includes a large number of participants, these participants may not truly be representative of the general population. To address this, we compared the anthropometric measurements and the frequencies of smoking 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 in terms of body structure than men from the overall Japanese population ($p < 0.05$) [10]. This difference should be considered when evaluating potential risk factors for men aged 70–74 years; factors such as body build, particularly weight, are known to be associated with metabolic risk factors and KOA. Therefore, our results may have underestimated the prevalence of these conditions. Second, the total number of subjects with confirmed OPLL was very small, which might make the results somewhat less credible. In the present study, we used logistic regression analysis to adjust for gender differences. When the total number of the objective variable, namely OPLL cases, is small, using the multivariate model to adjust for gender differences may be more useful than using a gender-specific analysis. This is because the total number of cases in a gender-specific analysis will be even smaller, which reduces the statistical power. Although the significant associations between OPLL and the plasma levels of pentosidine and between OPLL and DISH were observed only in men in the simple comparative analysis, the pentosidine levels and DISH remained significant factors associated with the presence of OPLL even in the logistic regression analysis with adjustments for gender. We interpreted this result to mean that the female sex might dilute the strength of the association between OPLL and DISH, but the tendency in both genders remained significant.

To clarify the effect of sex differences in the interaction among OPLL, pentosidine levels and DISH, the logistic regression analysis was performed in men and women separately

(Supplementary Table 1). In this logistic regression analysis, the presence of OPLL was significantly associated with the pentosidine levels and femoral neck BMD in men, but the association of OPLL with the presence of DISH was diluted to a marginal association ($p=0.080$). Further, since all male patients with DISH had radiographic LS, we could not evaluate the association between OPLL and LS. In women, the associations among OPLL, pentosidine levels and DISH were not significant. Although these results may indicate that the significant associated factors were observed only in men, they may even be skewed by the small number of female cases. Under these circumstances, it is difficult to distinguish which model should be used, i.e. logistic regression analysis or the multivariate model. It may be necessary to first include an adequate number of OPLL cases before this can be decided. To compensate for these limitations, we decided to include the urban cohort of the ROAD study in the OPLL survey. Thus, more participants will be included in the third ROAD survey planned from 2012 to 2013, and further detailed investigation regarding the risk factors for the presence, occurrence or exacerbation of OPLL may be possible.

In summary, the present study clarified that the prevalence of radiographic cervical OPLL in 1,562 individuals was 1.9 %, which was significantly higher in men than in women ($p=0.007$), but no association with age was observed. In logistic regression analysis, OPLL showed a significant association with the femoral neck BMD, presence of DISH and plasma pentosidine levels. Only one new case of radiographic OPLL was detected, but OPLL progressed in all affected subjects.

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Conflicts of interest None.

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ORIGINAL ARTICLE: SOCIAL RESEARCH,
PLANNING AND PRACTICE

Incidence of certified need of care in the long-term care insurance system and its risk factors in the elderly of Japanese population-based cohorts: The ROAD study

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Aim: To examine the incidence of certified need of care in the national long-term care insurance (LTCI) system, and to determine its risk factors in the elderly of Japanese population-based cohorts of the Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study.

Methods: Of the 3040 participants in the baseline examination of the ROAD study, we enrolled 1773 (699 men, 1074 women) aged 65 years or older who were not certified as in need of care level elderly at baseline. Participants were followed for incident certification of need of care in the LTCI system. Associated factors in the baseline examination with occurrence were determined by multivariate Cox proportional hazards regression analysis. Muscle dysfunction was defined in accordance with the European Working Group on Sarcopenia in Older People algorithm for screening sarcopenia.

Results: A total of 54 men and 115 women were certified as in need of care level elderly during the average 4.0-year follow up. The incidence was 2.0 and 2.5 per 100 person-years in men and women, respectively. Identified risk factors were region, age, body mass index <18.5 or ≥27.5 kg/m², grip strength, knee extension torque, usual gait speed, chair stand time and muscle dysfunction.

Conclusions: Both underweight and obesity, as well as low muscle strength and physical ability, are risk factors for certification of need of care. Considering muscle dysfunction is a risk factor for occurrence, screened individuals are recommended to receive early intervention programs regardless of muscle volume. **Geriatr Gerontol Int 2014; 14: 695–701.**

Keywords: activities of daily living, certification of need of care (*yukaigo-nintei*), disability, long-term care insurance system, prospective cohort study.

Introduction

Japan is a super-aged society experiencing an unprecedented aging of the population. The proportion of the population aged 65 years or older was 23% in 2010, and

is expected to reach 30.1% in 2024 and 39% in 2051.¹ This leads to an increasing proportion of disabled elderly requiring support or long-term care, imposing enormous economic and social burdens on the country. The Japanese Government started the national long-term care insurance (LTCI) system in 2000 based on the Long-Term Care Insurance Act.² The aim was to certify need of care level elderly, and to provide suitable care services according to the level of care required (seven levels, including requiring support [levels 1 and 2] and requiring long-term care [levels 1–5]). The total number of certified in need of care level elderly was reported to be 5 million in 2011.²

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Certification of need of care in the national LTCI system is an important outcome in Japan, not only because of its massive social and economic burdens, but also because it is urgently required to reduce its risk and decrease the number of disabled elderly requiring care in their activities of daily living (ADL). For establishment of an evidence-based prevention strategy, it is critically important to accumulate epidemiological evidence including the incidence of certified need of care and identification of risk factors. However, there have been no studies to clarify the incidence of certified need of care in the LTCI system or its risk factors using large-scale, population-based cohorts.

In 2005, we started a large-scale, population-based cohort study entitled the Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study with a total of 3040 participants, which aims to elucidate the environmental and genetic backgrounds of musculoskeletal diseases.^{3,4} The present study investigated the incidence of certified need of care in the national LTCI system, and determined its risk factors using a database from the ROAD study.

Methods

Participants

The present analysis was based on data collected from cohorts established in 2005 for the ROAD study. Details of the cohorts have been reported elsewhere.^{3,4} Briefly, we created a baseline database from 2005–2007, which included clinical and genetic information on 3040 residents of Japan (1061 men, 1979 women). Participants were recruited from resident registration listings in three communities, namely, an urban region in Itabashi, Tokyo, and rural regions in Hidakagawa and Taiji, Wakayama. Participants in the urban region in Itabashi were recruited from those of a cohort study,⁵ in which participants were randomly drawn from the register database of Itabashi ward residents, with a response rate of 75.6% in the group aged >60 years. Participants in the rural regions in Hidakagawa and Taiji were recruited from resident registration lists, with response rates of 68.4% and 29.3%, respectively, in the groups aged >60 years. Inclusion criteria were the ability to: (i) walk to the survey site; (ii) report data; and (iii) understand and sign an informed consent form. For the present study, we enrolled 1773 participants (699 men, 1074 women; mean age 75.4 years) aged 65 years or older who were not certified as need of care level elderly in the national LTCI system at baseline. All participants provided written informed consent, and the study was carried out with approval from the ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology.

Baseline procedures

Participants completed an interviewer-administered questionnaire containing 400 items that included life-style information, such as smoking habits, alcohol consumption and physical activity. At baseline, anthropometric measurements, including height and weight, were taken, and body mass index (BMI; weight [kg]/height² [m²]) was estimated based on the measured height and weight. Underweight was defined as BMI <18.5 and obesity as BMI ≥27.5, according to the 2004 consensus statement from the WHO regarding appropriate BMI for Asian populations.⁶ Grip strength was measured on bilateral sides using a handgrip dynamometer (TOEI LIGHT, Saitama, Japan); the higher measurement was recorded. Isometric peak knee extension torque was measured at a knee flexion angle of 90° using a dynamometer (GT-30; OG GIKEN, Okayama, Japan) twice in participants from the urban regional cohort (Itabashi, Tokyo); the higher measurement was recorded. The time taken to walk 6 m at usual walking speed in a hallway was recorded, and usual gait speed was calculated. Skeletal muscle dysfunction was defined as usual gait speed ≤0.8 m/s or grip strength <30 kg in men and <20 kg in women, according to the algorithm for screening sarcopenia recommended by the European Working Group on Sarcopenia in Older People (EWGSOP).^{7,8} The time taken for five consecutive chair rises without the use of hands was recorded in the rural regional cohorts (Hidakagawa and Taiji, Wakayama). Hands were folded in front of the chest with feet flat on the floor. Timing began with the command “Go”, and ended when the buttocks contacted the chair on the fifth landing.

Certification of need of care in the LTCI system

The nationally uniform criteria for long-term care need certification was established objectively by the Japanese Government, and certification of need of care level elderly is determined based on evaluation results by the Certification Committee for Long-term Care Need in municipalities in accordance with basic guidelines formulated by the Government. The process of eligibility for certification of need of care in the LTCI system was described in detail by Chen *et al.*⁹ An elderly person who requires help with ADL or the caregiver contacts the municipal Government to request official certification of care needs. After the application, a trained official visits the home to assess the current physical status of the elderly person, including the presence or absence of muscle weakness or joint contracture of limbs, and difficulties in sitting-up, standing-up, maintaining sitting or standing position, transferring from one place to another, standing on one leg, walking, bathing, dressing, and other ADL. Mental status, including dementia, is also assessed. These data are analyzed to calculate a

Table 1 Baseline characteristics of population at risk for certified need of care in the long-term care insurance system

	Entire cohort		Urban cohort		Rural cohort	
	Men	Women	Men	Women	Men	Women
No. participants	699	1,074	333	486	366	588
Age (years)	75.6 (5.1)	75.2 (5.3)	77.5 (3.7)	77.3 (3.8)	73.8 (5.5) [†]	73.5 (5.8) [†]
Height (cm)	160.9 (6.0)	147.9 (6.0)*	161.0 (5.8)	148.2 (5.4)*	160.8 (6.2)	147.7 (6.5)*
Weight (kg)	59.4 (9.1)	50.0 (8.3)*	59.4 (8.2)	49.8 (7.8)*	59.4 (9.9)	50.1 (8.8)*
BMI (kg/m ²)	22.9 (2.9)	22.8 (3.4)	22.9 (2.7)	22.7 (3.3)	22.9 (3.1)	22.9 (3.5)
BMI <18.5 (%)	6.2	8.0	6.1	7.9	6.3	8.0
BMI ≥27.5 (%)	5.7	9.3**	3.9	8.5**	7.4	9.9
Grip strength (kg)	30.4 (6.8)	19.4 (4.9)*	28.6 (6.1)	18.2 (4.1)*	31.9 (7.0) [†]	20.3 (5.2)* [†]
Knee extension torque (kgm)	–	–	79.6 (27.2)	54.8 (17.0)*	–	–
Usual gait speed (m/s)	1.17 (0.31)	1.10 (0.33)*	1.27 (0.24)	1.22 (0.24)*	1.08 (0.34) [†]	1.00 (0.36)* [†]
Chair stand time (s)	–	–	–	–	10.8 (3.7)	12.2 (5.4)*
Muscle dysfunction (%) [§]	48.7	56.0**	52.6	60.0**	45.2	52.6*** [†]
Smoking (%)	21.0	3.2**	19.2	3.0**	22.6	3.4**
Alcohol consumption (%)	61.2	23.0**	61.0	28.8**	61.3	18.4*** [†]

Except where indicated otherwise, values are mean (SD). **P* < 0.05 versus men in the corresponding group of the same cohort by unpaired Student's *t*-test. ***P* < 0.05 versus men in the corresponding group of the same sex by unpaired Student's *t*-test. †*P* < 0.05 versus urban cohort in the corresponding group of the same sex by unpaired Student's *t*-test. ‡*P* < 0.05 versus urban cohort in the corresponding group of the same sex by χ^2 -test. §Muscle dysfunction was defined as usual gait speed ≤0.8 m/s or grip strength <30 kg in men and <20 kg in women. BMI, body mass index; LTCI, long-term care insurance system.

standardized score for determination of the level of care needs (certified support, levels 1–2; or long-term care, levels 1–5). In addition, the primary physician of the applicant assesses physical and mental status, including information on diseases causing ADL disability and the extent of disabilities caused by them. Finally, the Certification Committee for Long-term Care Need reviews the data and determines the certification and its level.

Follow up and definition of incident certified need of care

After the baseline ROAD survey, participants who were not certified as need of care level elderly at baseline were followed for incident certification of need of care in the LTCI system. Incident certified need of care was defined as the incident certified 7 level, including requiring support (levels 1–2) and requiring long-term care (levels 1–5). Information on the presence or absence of certification of need of care and its date of occurrence were collected by the resident registration listings in three communities every year up to 2010, and were used for analyses in the present study.

Statistical analysis

All statistical analyses were carried out using STATA statistical software (STATA, College Station, TX, USA).

Differences in the values of the parameters between two groups were tested for significance using the non-paired Student's *t*-test and χ^2 -test. Factors associated with occurrence of certified need of care were determined using Cox proportional hazards regression analysis; hazard ratios (HR) and 95% confidence intervals (CI) were determined after adjusting for region, age, sex, and BMI.

Results

Of the 1773 participants who were not certified as in need of care level elderly at baseline, information on certification of need of care could be obtained in 1760 (99.3%) during the average 4.0-year follow up. A total of 54 men and 115 women were certified as in need of care level elderly in the national LTCI system; whereas, 1591 remained uncertified during the follow-up period. A total of 126 participants died, and eight moved away.

Table 1 shows the baseline characteristics of the population at risk for occurrence of certified need of care in the LTCI system. Although BMI was not significantly different between men and women in the entire, urban or rural cohorts, prevalence of obesity (BMI ≥27.5) was significantly higher in women than in men in the entire and urban cohorts. The prevalence of underweight was higher in women than in men in the entire,

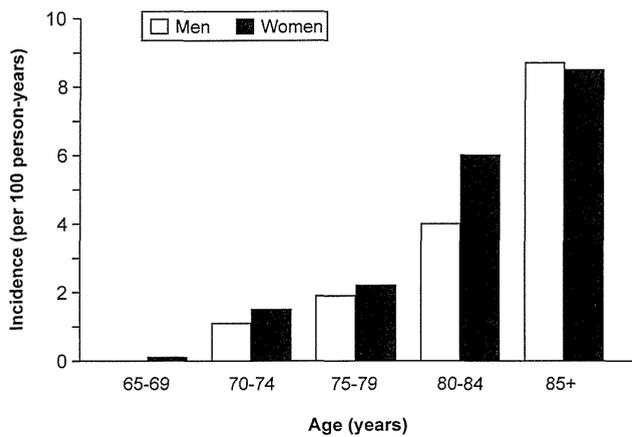


Figure 1 Incidence of certified need of care in the long-term care insurance system in men and women in each age stratum.

urban and rural cohorts; however, there was no significant difference. The prevalence of skeletal muscle dysfunction, determined by gait speed and grip strength, was significantly higher in women than in men in the entire, urban and rural cohorts.

Figure 1 shows sex- and age-distributions of the incidence of certified need of care in the LTCI system. Incidence was 2.3/100 person-years in the overall population of the entire cohort, and 2.0/100 person-years in men and 2.5/100 person-years in women. The incidence was very low in the age-stratum of 65–69 years, whereas, it tended to be markedly higher in the age-strata of 80 years and older in both sexes.

We then determined the risk factors for occurrence of certified need of care in the LTCI system. First, analysis was carried out using region, age, sex and BMI as explanatory variables in the Cox proportional hazards regression model (upper part of Table 2). Rural region and age were found to be risk factors for occurrence of certified need of care in the overall population. Sex and BMI were not significantly different. To further investigate the association between BMI and occurrence, we categorized BMI into three groups. Both underweight (BMI <18.5) and obesity (BMI ≥27.5) were found to be risk factors for occurrence of certified need of care, showing a U-shaped association. As for muscle strength and physical performance, handgrip strength, knee extension torque, usual gait speed, chair stand time and muscle dysfunction were found to be significantly associated with occurrence of certified need of care (lower part of Table 2). We carried out the same analyses in men and women separately (Table 2), and found results similar to those of the overall population.

Discussion

The present study investigated the incidence of certified need of care in the national LTCI system, and

Table 2 Hazard ratios and 95% confidence intervals for occurrence of certified need of care in the long-term care insurance system

	Overall population		Men		Women	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Region (rural vs urban)	1.15 (0.83–1.59)	1.61 (1.17–2.24) ^b	1.13 (0.65–1.96)	1.64 (0.94–2.86) ^b	1.15 (0.77–1.72)	1.59 (1.07–2.38) ^b
Age (+1 year)	1.17 (1.13–1.20)	1.17 (1.14–1.21) ^c	1.19 (1.12–1.26)	1.19 (1.13–1.26) ^b	1.16 (1.12–1.20)	1.16 (1.12–1.21) ^b
Sex (women vs men)	1.25 (0.90–1.74)	1.24 (0.89–1.73) ^d	–	–	–	–
BMI (+1 kg/m ²)	0.98 (0.93–1.03)	1.01 (0.96–1.06) ^e	0.93 (0.84–1.02)	0.96 (0.88–1.06) ⁱ	1.00 (0.94–1.06)	1.02 (0.97–1.08) ⁱ
≥18.5 or <27.5	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
BMI <18.5	2.10 (1.31–3.38)	1.77 (1.10–2.84) ^c	2.43 (1.09–5.40)	1.69 (0.75–3.82) ⁱ	1.93 (1.07–3.48)	1.79 (0.99–3.22) ^j
BMI ≥27.5	1.82 (1.13–2.93)	2.12 (1.32–3.43) ^c	1.39 (0.50–3.87)	1.91 (0.68–5.38) ⁱ	1.92 (1.12–3.29)	2.18 (1.27–3.75) ⁱ
Grip strength (+1 kg)	0.93 (0.91–0.95)	0.94 (0.91–0.97) ^f	0.91 (0.87–0.95)	0.94 (0.89–0.99) ^j	0.89 (0.85–0.92)	0.94 (0.89–0.98) ^j
Knee extension torque (+1 kgm)	0.97 (0.96–0.99)	0.97 (0.96–0.99) ^f	0.97 (0.95–0.99)	0.97 (0.95–0.99) ^j	0.97 (0.95–0.99)	0.97 (0.95–1.00) ^j
Usual gait speed (+0.1 m/s)	0.80 (0.77–0.85)	0.84 (0.79–0.90) ^f	0.81 (0.74–0.88)	0.83 (0.74–0.92) ^j	0.80 (0.76–0.85)	0.85 (0.78–0.92) ^j
Chair stand time (+1 s)	1.09 (1.07–1.12)	1.06 (1.03–1.10) ^f	1.18 (1.10–1.27)	1.11 (1.03–1.21) ^j	1.09 (1.06–1.11)	1.06 (1.02–1.09) ^j
Muscle dysfunction (yes vs no) ^a	2.91 (2.02–4.19)	1.71 (1.16–2.52) ^f	2.60 (1.45–4.68)	1.68 (0.91–3.09) ^j	3.07 (1.92–4.92)	1.72 (1.04–2.85) ^j
Smoking (yes vs no)	0.98 (0.58–1.68)	1.39 (0.79–2.43) ^f	1.18 (0.62–2.26)	1.54 (0.79–3.01) ^j	0.95 (0.30–2.99)	1.09 (0.35–3.47) ^j
Alcohol consumption (yes vs no)	0.71 (0.50–0.99)	0.83 (0.58–1.21) ^f	0.78 (0.45–1.35)	0.93 (0.53–1.61) ^j	0.70 (0.42–1.16)	0.76 (0.46–1.27) ^j

^aMuscle dysfunction was defined as usual gait speed ≤0.8 m/s or grip strength <30 kg in men and <20 kg in women. ^bAdjusted for age, sex and body mass index (BMI). ^cAdjusted for region, sex and BMI. ^dAdjusted for region, age and sex. ^eAdjusted for region, age and BMI. ^fAdjusted for age and BMI. ^gAdjusted for region and BMI. ^hAdjusted for region and age. ⁱAdjusted for region, age and BMI. ^jUrban region and men were used as references. CI, confidence interval; HR, hazard ratio.

determined its risk factors using Japanese population-based cohorts. Identified risk factors were region, age, underweight, obesity, handgrip strength, knee extension torque, usual gait speed, chair stand time and muscle dysfunction (determined by the EWGSOP algorithm for screening sarcopenia).

In the present study, we could not obtain information on causes of certified need of care in the LTCI system. Therefore, we could not analyze the direct association of each causing condition with such factors as anthropometric and physical performance measurements. The Government of Japan reported that the top five leading causes of certified need of care were cerebral stroke, dementia, asthenia as a result of older age, joint disease and fall-related fracture, comprising 71.6% of all causes in 2010.¹⁰ Based on these data, most of the causes of incident certification in the present study are inferred to be among the top five leading conditions.

Both low and high BMI were found to be risk factors for occurrence of certified need of care, showing an overall U-shaped association. This U-shaped association is similar to that between BMI and risk of death.^{11,12} The association between risk of death from cardiovascular disease and other causes, and BMI was reported to be U-shaped in East Asians,¹¹ whereas the risk of all-cause mortality versus BMI was also found to have a U-shaped association in Western European and North American populations.¹² High BMI is an established risk factor for chronic diseases, including hypertension, dyslipidemia and diabetes mellitus, which increase the risk of cerebral stroke.¹³ High BMI is also a major risk factor for knee osteoarthritis,¹⁴⁻¹⁷ which can cause ADL disability in the elderly.¹⁸ In contrast, low BMI is an established risk factor for osteoporosis and related fracture.¹⁹ It also might relate to asthenia, a condition of loss or lack of bodily strength as a result of chronic wasting disease. Underweight as a result of malnutrition or sarcopenia is suggested to be included in this category.

Other identified risk factors were handgrip strength, knee extension torque, usual gait speed, chair stand time and muscle dysfunction (determined by the EWGSOP algorithm for screening sarcopenia). Previous studies have reported that low muscle strength and physical performance were predictors of subsequent ADL disability in the elderly.²⁰⁻²³ The results of the present study are consistent with these previous reports. As many of the performance tests used in the present study are easy to carry out and evaluate, they can be utilized for screening elderly persons at high risk of certified need of care in the LTCI system. Those who were classified as having muscle dysfunction in the present study were at high risk of sarcopenia as well as certified need of care, regardless of muscle volume. Therefore, elderly persons screened by the EWGSOP algorithm are recommended to receive early interven-

tion programs for prevention of ADL disability and subsequent deterioration leading to certified need of care.

The Japanese Orthopedic Association proposed the concept of "locomotive syndrome" in 2007 for the promotion of preventive health care of locomotive organs.²⁴⁻²⁶ Locomotive syndrome refers to conditions under which the elderly have been receiving support or long-term care, or high-risk conditions under which they might soon require support or long-term care, that are caused by musculoskeletal disorders.²⁴⁻²⁶ Functional declines in locomotive organs, including muscle strength, walking speed and balancing ability, usually progress slowly and gradually. As such, it might be difficult for people to recognize this decline in their daily life. Therefore, it is of particular importance to raise awareness of the growing risk caused by these disorders, and to take action to improve and maintain the health of locomotive organs. Population approaches, including promotion of the concept of locomotive syndrome to both younger and older generations, are important, in addition to high-risk approaches, including identifying those at risk for certified need of care and practicing intervention programs to reduce the risk of certified need of care.

There were some limitations in the present study. As we could not obtain information on causing conditions, we could not determine the risk factors for occurrence of certified need of care with respect to each causing condition. Additional studies are necessary to identify those direct associations. In the present study, the rural region was at higher risk of incident certified need of care compared with the urban region. The reasons for this could include differences in available public and private transportation or delivery services regarding meals and commodities for the elderly. In addition to these, the threshold between certified and non-certified elderly might be different among municipalities, which could lead to regional differences. Although the Certification Committee for Long-term Care Need in each municipality determines certification in accordance with guidelines formulated by the Government, the Committee also has to consider assessment by the applicant's primary physician and objective evaluation results regarding physical and mental status, which could affect the threshold of certification. Another limitation was health bias. Participants at baseline in the present study were those who could walk to the survey site, and could understand and sign an informed consent form. As those who could not were not included in the analyses, the study participants do not truly represent the general population due to health bias. Therefore, incidence of certified need of care was most likely underestimated, which should be taken into consideration when generalizing the results of the present study.

In conclusion, the present study revealed the incidence of certified need of care in the national LTCI

system, and determined its risk factors using Japanese population-based cohorts. Both underweight and obesity were found to be risk factors for certified need of care, suggesting that maintenance of intermediate BMI is important for prevention. Low muscle strength and physical ability were also shown to be risk factors for certified need of care. Physical performance measures identified as predictors can be used as screening tools to identify high-risk individuals. Considering muscle dysfunction, screened by the EWGSOP algorithm, was a risk factor for occurrence, screened individuals are recommended to receive early intervention programs regardless of muscle volume. Further studies are necessary to develop intervention programs and to test their effectiveness, along with accumulation of epidemiological evidence, to prevent certified need of care and reduce the social and economic burdens associated with this condition.

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Disclosure statement

The authors declare no conflict of interest.

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Exercise habits during middle age are associated with lower prevalence of sarcopenia: the ROAD study

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Abstract

Summary The present cross-sectional study investigated the prevalence of sarcopenia and clarified its associated factors in 1,000 elderly participants of Japanese population-based cohorts. Exercise habit in middle age was associated with low prevalence of sarcopenia in older age, suggesting that it is a protective factor against sarcopenia in older age.

Introduction The present study investigated the prevalence of sarcopenia using the European Working Group on Sarcopenia in Older People (EWGSOP) definition, and clarified the association of sarcopenia with physical performance in the elderly participants of Japanese population-based cohorts of the Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study.

Methods We enrolled 1,000 participants (aged ≥ 65 years) from the second visit of the ROAD study who had completed assessment of handgrip strength, gait speed, and skeletal muscle mass measured by bioimpedance analysis. Presence of sarcopenia was determined according to the EWGSOP

algorithm. Information collected included exercise habits in middle age.

Results Prevalence of sarcopenia was 13.8 % in men and 12.4 % in women, and tended to be significantly higher according to increasing age in both sexes. Factors associated with sarcopenia, as determined by logistic regression analysis, were chair stand time (odds ratio [OR], 1.09; 95 % confidence interval [CI], 1.04–1.14), one-leg standing time (OR, 0.97; 95 % CI, 0.96–0.99), and exercise habit in middle age (OR, 0.53; 95 % CI, 0.31–0.90). Exercise habit in middle age was associated with low prevalence of sarcopenia in older age. Furthermore, linear regression analysis revealed that exercise habits in middle age were significantly associated with grip strength ($P < .001$), gait speed ($P < .001$), and one-leg standing time ($P = .005$) in older age.

Conclusions This cross-sectional study suggests that exercise habit in middle age is a protective factor against sarcopenia in older age and effective in maintaining muscle strength and physical performance in older age.

Keywords Elderly · Epidemiology · Exercise · Physical performance · Sarcopenia

Introduction

Sarcopenia is characterized by generalized loss of skeletal muscle mass and muscle strength and/or function in the elderly, causing multiple adverse health outcomes, including physical disability, poor quality of life, and death [1–6]. Although cross-sectional studies have investigated prevalence of sarcopenia [7–13], epidemiologic evidence using population-based samples is insufficient despite the urgent need for strategies to prevent and treat this condition.

Japan is a super-aged society, and the proportion of the aged population is increasing. The percentage of individuals

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aged ≥ 65 years was 23 % in 2010 and is expected to reach 30.1 % in 2024 and 39 % in 2051 [14]. The government of Japan reported that musculoskeletal disorders were present in 22.9 % of the entire population of those who were certified as requiring assistance or long-term care elderly in 2010 and were ranked first among its causes, together with joint diseases, falls, fractures, and spinal cord disorders [15]. For preventing and treating musculoskeletal disorders, there is an urgent need to develop and establish a prevention strategy and treatment programs that are effective in reducing the risk of disability among the elderly, which leads to requirement of assistance or long-term care. Although sarcopenia is a common musculoskeletal disease in the elderly, it is not clearly categorized [15]. There appears to be insufficient recognition of sarcopenia in daily clinical practice and society, leading to the disease being undiagnosed and untreated. One of the reasons may be the lack of a broadly accepted definition of sarcopenia until the European Working Group on Sarcopenia in Older People (EWGSOP) developed a practical clinical definition and consensus diagnostic criteria for this disease in 2010 [4]. There is a growing consensus that sarcopenia should not be defined merely on the basis of muscle mass but also with regard to muscle strength and function [4]. However, few epidemiologic studies have been based on the EWGSOP definition of sarcopenia using population-based samples, and no epidemiologic study has investigated the relationship between exercise habits in middle age and sarcopenia in older age.

The Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study is a prospective cohort study aimed at elucidating the environmental and genetic background of musculoskeletal diseases [16, 17]. The present study investigated the prevalence of sarcopenia using the EWGSOP definition, and clarified the association of sarcopenia with exercise habits in middle age and physical performance in the elderly participants of Japanese population-based cohorts of the ROAD study.

Methods

Participants

From 2005–2007, we began a large-scale population-based cohort study entitled Research on Osteoarthritis/osteoporosis Against Disability consisting of 3,040 participants in three regions (baseline study) [16, 17]. The ROAD study is a prospective cohort study with the aim of elucidating the environmental and genetic backgrounds of musculoskeletal diseases. It is designed to examine the extent to which risk factors for these diseases are related to clinical features of the diseases, laboratory and radiographic findings, bone mass, bone geometry, lifestyle, nutritional factors, anthropometric

and neuromuscular measures, and fall propensity. It also aims to determine how these diseases affect activities of daily living and quality of life of Japanese men and women. The subjects were residents of any one of three communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama. The inclusion criteria were as follows: ability to (1) walk to the clinic where the survey was performed, (2) provide self-reported data, and (3) understand and sign an informed consent form. Participants from the urban region were aged ≥ 60 years and were recruited from those enrolled in a randomly selected cohort study from the previously established Itabashi Ward residential registration database [18]. Invitation letters were distributed only to inhabitants whose names were listed on this database. Participants from Hidakagawa and Taiji were aged ≥ 40 years and were recruited from residential registration listings. Residents aged < 60 years from Itabashi and < 40 years from Hidakagawa and Taiji who were interested in participating in the study were also invited. A total of 99.8, 84.3, and 54.7 % of the participants were aged ≥ 60 years in Itabashi, Hidakagawa, and Taiji, respectively. The response rates in the groups aged ≥ 60 years were 75.6 % in Itabashi, 68.4 % in Hidakagawa, and 29.3 % in Taiji. Two-thirds of the 3,040 participants in the baseline survey were women, and their mean age was 1 year less than that of the male participants. No significant difference was observed in body mass index (BMI) between the sexes.

After the baseline study, a second survey was performed in the same communities from 2008 to 2010, in which 2,674 inhabitants (892 men, 1,782 women) aged 21–97 years participated (second visit) [19]. Invitation letters were distributed to the inhabitants whose names were listed on the baseline database of the ROAD study. In addition to the former participants, inhabitants aged ≥ 60 years from Itabashi and those aged ≥ 40 years from Hidakagawa and Taiji who were willing to participate in the ROAD survey performed in 2008–2010 were also included in the second visit. In addition, residents aged < 60 years from Itabashi and < 40 years from Hidakagawa and Taiji who were interested in participating in the study were invited to be examined as well at the baseline. The inclusion criteria were as follows: ability to (1) walk to the clinic where the survey was performed, (2) provide self-reported data, and (3) understand and sign an informed consent form. No other exclusion criteria were used. Thus, 2,674 residents (892 men and 1,782 women) aged 21–97 years participated in the second visit. Of the 2,674 participants, 1,846 individuals aged ≥ 65 years visited the clinic and underwent an examination at the survey site located in Hidakagawa (504 individuals), Taiji (391 individuals), the University of Tokyo Hospital (132 individuals), or Tokyo Metropolitan Geriatric Hospital (819 individuals). For participants from Itabashi, the survey site was randomly assigned to either the University of Tokyo Hospital or Tokyo