of thoracolumbar vertebrae Th5-L5 were used for diagnosis (Initial X-ray survey). Radiographic examination was again performed on subjects who provided consent after 10 years. Lateral images of thoracolumbar vertebrae Th5-L5 were again used for diagnosis (2nd X-ray survey). Lateral spinal radiographs were examined for the presence of one or more vertebral fractures (VFx) between Th5–L5, using the criteria determined by the Japan Bone and Mineral Society (Fig. 1) [17]. According to these criteria, measurement of anterior, middle and posterior heights on lateral radiography of the thoracic and lumbar spine is required, to determine ratios defining the anterior wedge, biconcave and compound dimensions of the vertebral bodies. Diagnosis of VFx on all radiographs was performed by the same experienced orthopedic doctor (HK). In the present study, cumulative incidence over 10 years was detected by dividing the number of incident cases by the number of participants in the follow-up study, and cases with previous VFx were excluded from both numerators and denominators. In this analysis, cumulative incidence of cases with first VFx was detected.

QOL postal survey

The QOL questionnaire postal survey was performed in 2002. To select QOL items, the Euro Qol EQ5D questionnaire [18] translated into Japanese was used, comprising the following two parts: a 5-dimensional health state classification; and a visual analogue scale (VAS) called the "thermometer" [19]. The 5-dimensional healthcare classification included questions on the status of morbidity, self-care, usual activities, pain/discomfort and anxiety/depression. Participants were asked to indicate current health status by ticking the most appropriate of three statements about each of five QOL dimensions. Each statement represents an increasing degree of severity. These results were coded and converted to a score of utility using the tables of values. The VAS "thermometer" represents a self-rated scale of current health-related QOL. The endpoint of 100 at the top indicates the best imaginable health state, and 0 at the bottom indicates the worst imaginable health state at that time.

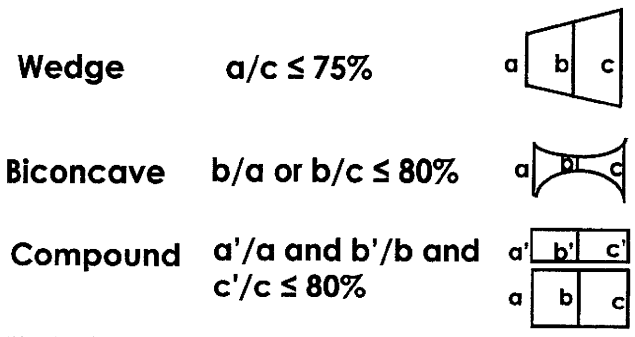

Fig. 1 Diagnostic criteria of vertebral fractures

Statistical analysis

Statistical analyses were performed using SPSS statistical software (SPSS, USA) and STATA software (STATA, USA). Differences were tested for significance using ANOVA for comparison among multiple groups and Scheffe's LSD test for pairs of groups. Significant items were selected, and multiple regression analysis was performed with adjustment of suitable variables.

Results

Eligible participants

From the whole cohort of 1,543 inhabitants (716 men, 827 women), 50 men and 50 women in each decade age group between 40–79 years (a total of 400 participants) were recruited for baseline bone densitometry in 1990 (baseline BMD cohort).

To evaluate the representativeness of subjects in the baseline BMD cohort compared to the whole cohort, the prevalence of 125 items of the self-administered questionnaire, results of physical measurements and blood examination were compared between members of the BMD and whole cohorts [14]. As a result, prevalence of lifestyle factors such as smoking and drinking were identical among BMD and whole cohorts. In addition, no significant differences existed in frequency distribution of the following items favorable to the maintenance of good health among BMD and whole cohorts: sleeping 7–8 h/day; exercise and sports >1 h/day; walking >30 min/day; eating regularly; reduction of salt intake compared with age 30; less stress; less anger. Regarding medical examinations, no significant differences in blood pressure classified by age and sex were seen between cohorts. Moreover, no abnormal values in serum calcium or phosphorus were observed. In view of these findings, subjects in the BMD study were considered to have been selected adequately from the whole cohort.

A total of 299 of 400 participants (137 men, 162 women; 74.8%) completed the follow-up survey after 10 years. Loss of 101 participants was due to following: death, n=55 (37 men, 18 women); moved away from Miyama, n=16 (8 men, 8 women); illness, n=13 (4 men, 9 women); busy, n=8 (8 men); refused to participate further, n=5 (5 men); and away from the area at the time of follow-up, n=4 (1 man, 3 women). Analysis was performed on the 299 subjects who had participated in all surveys performed in 1990, 1993, 1997 and 2000.

A comparison of physical characteristics between completers and non-completers has been described elsewhere [20], and is briefly summarized here. Height, weight and

BMI classified by age-strata and sex were identical between completers and non-completers, while mean age of female completers in their 70s was significantly younger than that of female non-completers (completers, 71.7 years (standard deviation (SD), 1.8 years) vs. non-completers 75.1 years (SD; 2.8 years); $p<0.001$).

Table 1 shows the characteristics including anthropometric factors and BMDs at the time of baseline measurement for participants who completed the 10-year follow-up (Table 1). Mean height and weight of the remaining participants were smaller according to age, while BMI did not differ significantly for both men and women in all age groups except men in their 70s.

Height loss and bone loss

Table 2 shows mean change of height, weight, BMI and change rate of BMDs over 10 years by age and gender (Table 2). Height and weight of men and women decreased in all age strata, and these decreases were greatest in subjects in their seventies. BMI in the 50s, 60s and 70s were decreased over 10 years in both genders, but no significant differences were seen among age-strata. BMDs at the lumbar spine and femoral neck decreased except for BMD at the lumbar spine in men.

To clarify associations between height, height change and changes in BMD, multiple regression analysis was performed. Rate of change of BMD (%/year) was used as an objective factor and height at baseline (cm) or change of height (cm/10 years) were used as explanatory factors. Analysis was performed after adjustment for age and female menstrual status at baseline (0, regular; 1, irregular; 2, menopause). In both men and women, no significant relationship was identified between bone loss and height at baseline (lumbar spine: men, $\beta=-0.046$, standard error of the mean (SE)=0.011, P=0.653, $R^2=0.036$; women, $\beta=-0.042$, SE=0.014, P=0.652, $R^2=0.032$; femoral neck: men, $\beta=0.143$, SE=0.014, P=0.149, $R^2=0.125$; women: $\beta=0.078$, SE=0.014, P=0.397, $R^2=0.043$).

Regarding the association between height loss and bone loss over 10 years, no significant relationship was identified between height change and rate of change of BMD at the lumbar spine and femoral neck after adjusting for age in men (lumbar spine: $\beta=0.058$, SE=0.031, P=0.501, $R^2=0.038$; femoral neck: $\beta=0.100$, SE=0.038, P=0.228, $R^2=0.121$). In contrast, among women, significant positive associations were noted between height change and change rate of BMD at the lumbar spine after adjusting for age ($\beta=0.221$, SE=0.039, P=0.012, $R^2=0.069$), while no significant relationship was noted between height change and change rate at the femoral neck ($\beta=0.107$, SE=0.039, P=0.229, $R^2=0.048$).

Height loss and vertebral fractures

As reported elsewhere [21], 32 men and 35 women had suffered from previous VFx at the initial survey. Cumulative incidences of first VFx at follow-up for subjects in their 40s, 50s, 60s and 70s were thus 2.9%, 2.8%, 8.6% and 21.1% in male completers, respectively, and 2.1%, 7.0%, 18.9% and 31.3% in female completers, respectively. Cumulative incidence of first VFx among participants during follow-up increased with age in both men and women, and was higher in women than in men in all age-strata except the 40s.

Table 3 shows differences in height at baseline and height loss between the incident group and non-fracture group. Both height and height loss over the 10 years were

Table 1 Characteristics at the baseline measurement of participants completed 10-year follow-up

				Anthropometric factors			Bone mineral density (g/cm^2)	
Birth cohort	Age strata	N	Age (years)	Height(cm)	Weight(kg)	BMI (kg/m^2)	L2-4	Femoral neck
Men								
1940–1949	40–49	36	44.1 (3.1)	166.5 (5.9)	64.4 (8.9)	23.1 (2.3)	1.19 (0.17)	0.98 (0.16)
1930–1939	50–59	41	53.9 (2.6)	162.0 (5.7)[a]	60.2 (8.0)	22.9 (2.4)	1.15 (0.20)	0.90 (0.18)
1920–1929	60–69	38	63.2 (2.8)	159.4 (5.4)[a]	56.1 (7.5)[a]	22.0 (2.4)	1.03 (0.19)[a]	0.82 (0.12)[ab]
1910–1919	70–79	22	73.2 (2.7)	155.3 (6.5)[ab]	50.0 (8.4)[ab]	20.6 (2.6)[ab]	1.03 (0.20)[a]	0.79 (0.11)[ab]
Women								
1940–1949	40–49	49	44.7 (3.1)	152.5 (4.7)	53.3 (8.4)	22.9 (2.8)	1.18 (0.16)	0.88 (0.12)
1930–1939	50–59	46	54.8 (2.6)	149.6 (5.3)	50.3 (7.4)	22.4 (2.8)	0.99 (0.18)[a]	0.75 (0.12)[a]
1920–1929	60–69	40	64.4 (2.8)	147.4 (5.1)[a]	47.4 (6.8)[a]	21.8 (3.0)	0.86 (0.20)[ab]	0.69 (0.11)[ab]
1910–1919	70–79	27	71.7 (1.8)	143.1 (5.5)[ab]	45.4 (7.7)[a]	22.1 (3.0)	0.79 (0.16)[ab]	0.65 (0.09)[ab]

Mean (SD)
a: Significantly different from values of the birth cohort group born in 1940–1949
b: Significantly different from values of the birth cohort group born in 1930–1939

Table 2 Changes in height, weight, BMI and change rate in bone mineral densities over 10 years by age and gender

Age at initial survey	Change rate of anthropometric factors			Change rate of bone mineral density	
Age strata (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	L2–4 (%/year)	Femoral neck (%/year)
Men					
40–49	−0.73 (2.21)	−0.21 (5.09)	0.17 (2.20)	0.17 (0.69)	−0.26 (0.86)
50–59	−0.54 (2.09)	−0.83 (3.69)	−0.18 (1.38)	0.55 (0.58)	−0.13 (0.84)
60–69	−1.19 (2.41)	−3.01 (4.80)	−0.86 (1.84)	0.01 (0.89)[b]	−0.75 (0.97)[b]
70–79	−1.54 (1.72)	−3.05 (3.88)	−0.84 (1.65)	−0.16 (0.68)[b]	−1.17 (1.09)[ab]
Women					
40–49	−0.69 (1.21)	−0.33 (3.22)	0.06 (1.39)	−0.87 (0.71)	−0.53 (0.70)
50–59	−1.37 (1.18)	−1.74 (3.64)	−0.35 (1.69)	−0.83 (0.75)	−0.53 (0.71)
60–69	−2.06 (2.08)[a]	−2.44 (3.55)[a]	−0.58 (1.69)	−0.48 (0.71)	−0.50 (0.87)
70–79	−3.65 (2.83)[abc]	−3.09 (3.48)[a]	−0.42 (1.76)	−0.48 (1.48)	−1.16 (1.32)[abc]

Mean (SD)
a: Significantly different from values of the age-group in their 40s
b: Significantly different from values of the age-group in their 50s
c: Significantly different from values of the age-group in their 60s

also greater in the group with VFx than without VFx. To clarify associations between height or height change and incidence of VFx after excluding the effects of age, logistic regression analysis was performed. We utilized new VFx over 10 years (1: yes; 0: no) as an objective factor and height at baseline (cm) or change of height (cm/10 years) as explanatory factors. Analysis was performed after adjusting for age and female menstrual status at baseline (0: regular; 1: irregular; 2: menopause). After logistic regression analysis, no significant relationship was identified between VFx and height at baseline in men and women (men: odds ratio (OR) 0.93, 95% confidence interval (CI) 0.81–1.05, P=0.24; women: OR 0.97, 95% CI 0.87–1.08, P=0.58). Furthermore, a non-significant relationship was seen between cumulative incidence of VFx and height loss in men and women (men: OR 1.31, 95% CI 1.00–1.71, P=0.051; women: OR 1.20, 95% CI 0.94–1.53, P=0.14).

Table 3 Comparison of height (cm) at baseline and height loss between the group with new vertebral fractures and the no fracture group

		VFx* over 10 years		
		No (n=116)	Yes (n=9)	P (Yes vs. No)
Men	Height (cm)	161.8 (6.49)	156.4 (7.76)	0.014
	Height loss (cm/10 years)	0.87 (2.08)	2.59 (2.23)	0.019
		No (n=128)	Yes (n=16)	
Women	Height (cm)	149.7 (5.75)	145.9 (6.43)	0.015
	Height loss (cm/10 years)	1.33 (1.78)	2.88 (2.26)	0.002

*VFx: vertebral fractures

Height loss and QOL

Among the 299 subjects who participated in the latest follow-up survey in 2000, 212 answered the QOL questionnaire distributed in 2002 (94 men, 118 women; 70.9%).

Figures 2 and 3 show mean values for utility in EQ5D health states and VAS scores classified by age and gender. Mean utility for EQ5D in men in their 40s (n=30), 50s (n=33), 60s (n=25) and 70s (n=6) were 0.95, 0.87, 0.88 and 0.83, respectively, compared to 0.90, 0.85, 0.81 and 0.77 in women in their 40s (n=42), 50s (n=32), 60s (n=31) and 70s (n=13). VAS values in men were 76.6, 75.1, 72.4 and 63.8, respectively, compared to 77.6, 73.9, 67.6 and 71.7, respectively, in women. Utility of EQ5D decreased according to age in both men and women, while mean VAS scores were lowest for women in their 60s.

We utilized multiple regression analysis using utility of EQ5D health states or VAS scores as an objective factor and height at baseline (cm) or change of height (cm/10 years) as explanatory factors to clarify associations between height and QOL. Analysis was performed after adjusting for age and female menstrual status at baseline

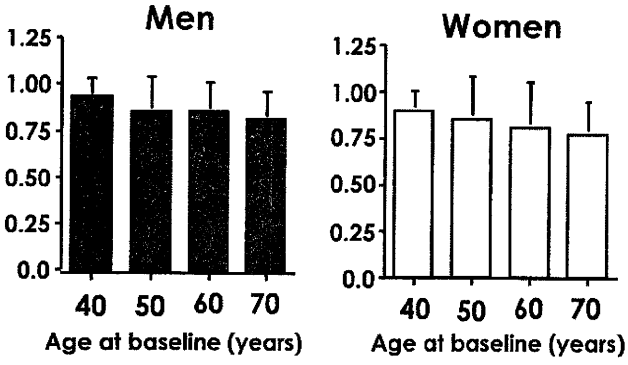

Fig. 2 QOL score classified by age and gender

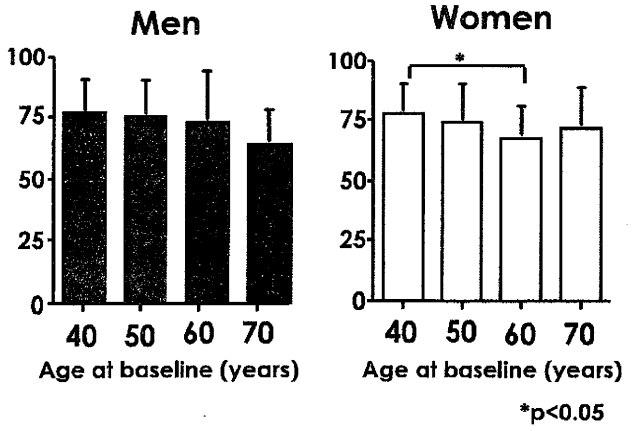

Fig. 3 VAS scores classified by age and gender

(0: regular; 1: irregular; 2: menopause). In both men and women, no significant relationship was identified between utility of EQ5D and height at baseline (men: β=−0.148, SE=0.003, P=0.202, R^2=0.076; women: β=0.127, SE=0.004, P=0.235 R^2=0.048), and height change (men: β=−0.078, SE=0.008, P=0.452, R^2=0.065; women: β=0.053, SE=0.010, P=0.608, R^2=0.038). Regarding VAS scores, height at baseline among men and women was not significantly associated VAS scores (men: β=−0.148; SE=0.003, P=0.202, R^2=0.076; women: β=0.066, SE=0.255, P=0.532, R^2=0.092). In addition, no significant associations were identified between utility of VAS scores and height change (men: βa=−0.148, SE=0.003, P=0.202, R^2=0.076; women: β=0.142, SE=0.698, P=0.160, R^2=0.105).

Discussion

The present study clarified associations between height, height change and bone loss and cumulative incidence of VFx. Furthermore, we assessed the usefulness of height and height change as predictors of future QOL. As a result, we identified significant positive associations between height change and change rate of BMD at the lumbar spine in women after adjusting for age and menstrual status, while no significant relationships were found between height or height change at the femoral neck in either men or women. Regarding associations between height, height change and cumulative incidence of first VFx, both height and height loss over the 10 years were also greater in the group with VFx than in the group without VFx, but the association was less significant in logistic regression analysis after adjusting for age. No significant relationships existed between height, height change and future QOL in men or women.

Particularly among anthropometric measurements, light weight [5–8], weight loss [9, 10] and low BMI [11–13] could suggest a risk of osteoporosis and osteoporotic fractures. Conversely, few investigations have reported that height and height loss are associated with low BMD or bone loss. We have already reported that tall height is associated with greater bone loss over 3 years [22]. Twiss et al. [23] reported that actual height loss is associated with risk factors of osteoporosis, while Thornton et al. [24] evaluated relationship between height change and bone mineral density among 168 healthy women at 50- to 65-years-old, and reported no significant relationships between height change and BMD. Kantor [25] reviewed cross-sectional data from 2,108 women referred for a bone density scan and reported that a height loss of ≥2 inches offers a highly significant predictor of osteoporosis at the hip [25]. As mentioned, investigations into associations between height and bone loss have yielded controversial results, and no data from follow-up studies over periods as long as 10 years have been available. The present study clarified that greater height loss was associated with greater bone loss at the lumbar spine in women. This means that height loss might offer a predictor for greater bone loss, thus indicating a potential high-risk group for future osteoporosis in women. Conversely, the present study failed to identify any significant association between height loss and bone loss at the lumbar spine in men, which is artificial due to the difficulties in measuring BMD at the lumbar spine in men. As observed in the BMD cohort, 35.1% of men and 13.3% of women were diagnosed with osteophytosis more than grade 3 according to Nathan's classification [26, 27]. Such osteophytes might lead to overestimation of BMD in men.

Regarding the relationship between height loss and osteoporotic fractures, Meyer et al. [11] compared mean height among participants of population-based cohort studies established in different countries in Europe, and found that participants in Oslo were taller than those in other European countries. They noted that the taller height of community-dwelling inhabitants might contribute to the higher incidence of hip fracture in Finland, although this suggestion was based on ecological data. Fujiwara et al. [28] suggested that the presence of more than one column of VFx will lead to a decrease of about 2 cm in height. The present study found both height and height loss over the 10 years were also greater in the group with VFx than in the group without VFx, but failed to identify any statistically significant association between height loss and VFx. This might be because the sample size of the BMD cohort was insufficient to detect a significant association. However, height loss (cm/10 years) tended to increase the OR of VFx in both men and women. Loss of height may represent an important clinical sign of vertebral deformation and/or fracture in postmenopausal women and elderly men. Relationships between BMD at the femoral neck and hip fracture were not able to be analyzed because of the low numbers of new hip fractures in subjects. A larger

epidemiological study would be needed to clarify associations between height loss and future osteoporotic fractures.

Regarding relationships between QOL, height and height loss, Martin et al. [29] found that height loss and kyphosis in women are significantly associated with increased physical difficulty in activities of daily life. In addition, some reports have described the influence of osteoporotic VFx on QOL [30–32]. These investigations have shown that patients with higher grades of vertebral deformities displayed low QOL, suggesting that the results of VFx such as height loss are related to QOL, but the direct influence of height loss on QOL remains unclear. The present study could not find any significant association between height loss and QOL, so we concluded that QOL in patients with osteoporosis is impaired by postural deformities, particularly by whole kyphosis, and that spinal mobility exerts a strong effect on QOL in these patients.

Conclusions

The present study identified significant positive associations between height change and change rate of BMD at the lumbar spine in women, while no significant relationships were found between height, height change, cumulative incidence of VFx and future QOL.

In conclusion, changes in measured height might offer a cost-saving indicator of bone loss. Measurement of height should be considered as one potential component in determining risk of comprehensive osteoporosis, but further consideration is required before utilizing this approach as a predictor of future osteoporotic fracture and QOL.

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References

1. Hosoda Y, Fujiwara S (1992) The epidemiology of osteoporosis in Japan. J Epidemiol 2(suppl):205–213
2. Hashimoto T, Sakata K, Yoshimura N (1997) Epidemiology of osteoporosis in Japan. Osteoporos Int 7(suppl):99–102
3. Orimo H, Hashimoto T, Sakata K, Yoshimura N, Seino Y, Emi M, Hada A, Suzuki T, Hosoi T, Miyao M, Research Group for Risk Factors for Prevention of Osteoporosis, Longevity Science General Research Project, Ministry of Health and Welfare, (Director Orimo H) (1999) Results of the 3rd nation-wide survey of femoral neck fracture. Estimation of the number of new patients in 1997 and changes during the past 10-year period. Nihon Iji Shinpo (Japan Medical Journal) 3916:46–49 (in Japanese)
4. Yosihmura N, Suzuki T, Hosoi T, Orimo H (2005) Epidemiology of hip fracture in Japan: incidence and risk factors. J Bone Miner Metab 23:78–80
5. Wardlaw GM (1996) Putting body weight and osteoporosis into perspective. Am J Clin Nutr 63 (3 Suppl):433–436
6. Yoshimura N, Hashimoto T, Morioka S, Sakata K, Kasamatsu T, Cooper C (1998) Determinants of bone loss in a rural Japanese community. The Taiji Study. Osteoporos Int 8:604–610
7. Dennison E, Eastell R, Fall CH, Kellingray S, Wood PJ, Cooper C.(1999) Determinants of bone loss in elderly men and women: a prospective population-based study. Osteoporos Int 10:384–391
8. Wildner M, Peters A, Raghuvanshi VS, Hohnloser J, Siebert U (2003) Superiority of age and weight as variables in predicting osteoporosis in postmenopausal white women. Osteoporos Int 14:950–956
9. Nguyen TV, Sambrook PN, Eisman JA. (1998) Bone loss, physical activity, and weight change in elderly women: the Dubbo Osteoporosis Epidemiology Study. J Bone Miner Res 13:1458–1467
10. Tsunenari T, Yamada S, Kawakatsu M, Negishi H, Tsutsumi M (1995) Menopause-related changes in bone mineral density in Japanese women. A longitudinal study. Calcif Tissue Int 56:5–10
11. Meyer HE, Falch JA, O'Neill T, Tverdal A, Varlow J (1995) Height and body mass index in Oslo, Norway, compared to other regions of Europe: do they explain differences in the incidence of hip fracture? European Vertebral Osteoporosis Study Group. Bone 17:347–350
12. Nguyen TV, Center JR, Eisman JA (2000) Osteoporosis in elderly men and women: effects of dietary calcium, physical activity, and body mass index. J Bone Miner Res 15:322–331
13. Korpelainen R, Korpelainen J, Heikkinen J, Vaananen K, Keinanen-Kiukaanniemi S (2006) Lifelong risk factors for osteoporosis and fractures in elderly women with low body mass index-A population-based study. Bone 39:385–391
14. Kasamatsu T, Morioka S, Hashimoto T, Kinoshita H, Yamada H, Tamaki T (1991) Epidemiological study on bone mineral density of inhabitants in Miyama Village, Wakayama Prefecture (Part 1). Background of study population and sampling method. J Bone Miner Metabol 9(suppl):50–55
15. Kinoshita H, Danjoh S, Yamada H et al (1991) Epidemiological study on the bone mineral density of inhabitants in Miyama Village, Wakayama Prefecture (part II) Bone mineral density of the spine and proximal femur. J Bone Miner Metab 9(suppl):56–60
16. Yoshimura N, Kakimoto T, Nishioka M, Kishi T, Iwasaki H, Niwa T, Morioka S, Sakata T, Hashimoto T (1997) Evaluation of reproducibility of bone mineral density measured by dual energy X-ray absorptiometry (Lunar DPX-L). J Wakayama Medical Society 48:461–466
17. Yoshimura N, Kinoshita H, Danjoh S, Yamada H, Tamaki T, Morioka S, Kasamatsu T, Hashimoto T, Inoue T (1995) Prevalence of vertebral fractures in a rural Japanese population. J Epidemiology 5:171–175
18. EuroQol Group (1990) EuroQol: A new facility for the measurement of health-related quality of life. Health Policy 16:199–208
19. Ikeda S, Ikegami N (on behalf of the Japanese EuroQol Tariff Project) (1999) Health status in Japanese population, Results from Japanese EuroQol Study. Iryou-to-Kagaku 9:83–92 (in Japanese)
20. Yoshimura N, Kinoshita H, Danjoh S, Takijiri T, Morioka S, Kasamatsu T, Sakata K, Hashimoto T (2002) Bone loss at the lumbar spine and the proximal femur in a rural Japanese community, 1990–2000: The Miyama study. Osteoporos Int 13:803–808
21. Yoshimura N, Kinoshita H, Oka H, Muraki S, Mabuchi A, Kawaguchi H, Nakamura K (2006) Cumulative incidence and changes in prevalence of vertebral fractures in a rural Japanese

community: a 10-year follow-up of the Miyama Cohort. Archives Osteoporosis, DOI 10.1007/s11657-006-0007-0
22. Yoshimura N (1996) Incidence of fast bone losers and factors affecting changes in bone mineral density - A cohort study in a rural Japanese community-. J Bone Miner Metab 14:171–177
23. Twiss JJ, Dillon AL, Konfrst JM, Stauffer J, Paulman A (2002) The relationship of actual height loss with health-seeking behaviors and risk factors in perimenopausal and menopausal women. J Am Acad Nurse Pract 14:131–137
24. Thornton MJ, Sedlak CA, Doheny MO (2004) Height change and bone mineral density: revisited. Orthop Nurs 23:315–320
25. Kantor SM, Ossa KS, Hoshaw-Woodard SL, Lemeshow S (2004) Height loss and osteoporosis of the hip. J Clin Densitom 7:65–70
26. Nathan H (1962) Osteophytes of the vertebral column, an anatomical study of their development according to age, race, and sex with considerations as to their etiology and significance. J Bone and Joint Surg 44:243
27. Yoshimura N, Saika A, Oka H (2006) The study on the causality between osteoporosis and osteoarthritis. Osteoporos Jpn 14:691–695 (in Japanese)
28. Fujiwara S (2006) Clinical sign-height loss and vertebral deformity. Nippon Rinsho 64:1610–1614 (in Japanese)
29. Martin AR, Sornay-Rendu E, Chandler JM, Duboeuf F, Girman CJ, Delmas PD (2002) The impact of osteoporosis on quality-of-life: the OFELY cohort. Bone 31:32–36
30. Fechtenbaum J, Cropet C, Kolta S, Horlait S, Orcel P, Roux C (2005) The severity of vertebral fractures and health-related quality of life in osteoporotic postmenopausal women. Osteoporos Int 16:2175–2179
31. Miyakoshi N, Itoi E, Kobayashi M, Kodama H (2003) Impact of postural deformities and spinal mobility on quality of life in postmenopausal osteoporosis. Osteoporos Int 14:1007–1012
32. Tanaka K, Yoshizawa M, Yoh K (2005) Improvement of QOL in osteoporotic patients by calcitonin treatment. Clin Calcium 15:174–178 (in Japanese)

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Fully automatic quantification of knee osteoarthritis severity on plain radiographs

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Summary

Objective: Although knee osteoarthritis (OA) is a major public health issue causing chronic disability, there is no objective or accurate method for measurement of the structural severity in general clinical practice. Here we have established a fully automatic program KOACAD (knee OA computer-aided diagnosis) to quantify the major OA parameters on plain knee radiographs, validated the reproducibility and reliability, and investigated the association of the parameters with knee pain.

Methods: KOACAD was programmed to measure joint space narrowing at medial and lateral sides, osteophyte formation, and joint angulation. Anteroposterior radiographs of 1979 knees of a large-scale cohort population were analyzed by KOACAD and conventional categorical grading systems.

Results: KOACAD automatically measured all parameters in less than 1 s without intra- or interobserver variability. All parameters, especially medial joint space narrowing, were significantly correlated with the conventional gradings. In the parameters, osteophyte formation was associated with none of the joint space parameters, suggesting different etiologic mechanisms between them. Multivariate logistic regression analysis after adjustment for age and confounding factors revealed that medial joint space narrowing and varus angulation of knee joints were risk factors for the presence of pain (594/1979 knees), while neither lateral joint space nor osteophyte area was.

Conclusion: KOACAD was shown to be useful for objective, accurate, simple and easy evaluation of the radiographic knee OA severity in daily clinical practice. This system may also serve as a surrogate measure for the development of disease-modifying drugs for OA, just as bone mineral density does in osteoporosis.

Key words: Osteoarthritis, Knee, Diagnosis, Computer-aided diagnosis, Imaging, Plain radiograph.

Introduction

Due to the rapidly increasing fraction of aging people today, osteoarthritis (OA) is now considered as a major public health issue causing chronic disability in most developed countries. It is estimated that up to 10% of the entire world population, and more than 50% of those aged over 50 years, are suffering from OA[1]. Knee OA, affecting about 30% of those over 65 years and as often associated with disability as heart and chronic lung diseases[2,3], is characterized by pathological features including joint space narrowing, osteophyte formation, and joint angulation. Although OA and osteoporosis are the two major skeletal disorders with strong social impact[4], OA falls far behind osteoporosis in the assessment of its disease severity and in the development of disease-modifying drugs. This is mainly due to the lack of an objective and accurate method to evaluate the structural severity and thereby to assess the efficacy of drugs as surrogate measures like bone mineral density (BMD) in osteoporosis.

Although magnetic resonance imaging (MRI) with high resolution has been rapidly advanced as a promising technique, it is still too laborious and expensive to perform in general clinical practice or in population-based epidemiologic studies, and the interpretation remains controversial as a primary end-point in clinical trials of the disease-modifying drugs[5–7]. Biochemical markers of cartilage turnover are being tested to measure the disease progression; however, their validation as a surrogate measure will require significant additional work[5,8]. Hence, plain radiography is considered the gold standard as a method that is non-invasive, inexpensive, convenient, simple, and fast to use in assessing OA severity. The most conventional system to grade the radiographic severity has been the Kellgren/Lawrence (K/L) grading[9]. However, this categorical system is limited by incorrect assumptions that progression of distinct OA features like joint space narrowing and osteophyte formation is linear and constant, and that their relationships are proportional. Since the system emphasizes the development of osteophytes, it is unclear how to handle knees with severe joint space narrowing but no osteophyte formation. To overcome the problem,

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a radiographic atlas of individual features was published by the OA Research Society International (OARSI) in 1995[10] and a revised version in 2007[11]. This system separately evaluates joint space narrowing and osteophyte formation at the medial and lateral tibiofemoral compartments on radiographs; however, the grading is still limited in reproducibility and sensitivity due to the subjective judgment of individual observers and the categorical classification into four-grade (0–3) scales. Although several semi-automatic methods for objective measurement with continuous variables of joint space or angle using computer-assisted systems have recently been developed, there still remain intra- and interobserver variabilities since initial operations like identifying points or drawing lines must be manually performed[12–16].

The present study has developed a novel computer program, KOACAD (knee OA computer-aided diagnosis), which for the first time has realized a fully automatic measurement of major parameters of knee OA: joint space area (JSA) and the minimum joint space width (mJSW) at medial and lateral sides, osteophyte area, and tibiofemoral angle (TFA) on plain anteroposterior radiographs. We examined the reproducibility and reliability of KOACAD by comparing it with conventional grading systems and semi-automatic measurements.

Arthritis is the most common cause of pain in the elderly[17], and knee pain is the principal clinical symptom of knee OA. Although much effort has been devoted toward a definition of knee pain, the correlation with radiographic severity of the knee OA was not as strong as one would expect[18–20]. Hence, this study finally sought to identify radiographic factors related to knee pain by examining the association of the KOACAD parameters with the presence of pain using a baseline database of our large-scale OA cohort study ROAD (research on OA against disability).

Subjects and methods

SUBJECTS

The ROAD study is a nationwide OA cohort study that started in 2005, and is constituted of four cohorts. So far, we have completed creation of a baseline database including clinical and genomic information of 3040 participants in three cohorts in urban, mountainous, and seacoast areas. The database includes anteroposterior and lateral radiographs of bilateral knees of all participants. For evaluation of the KOACAD system, we used 1979 anteroposterior radiographs from 2002 knees of 1001 participants of the urban cohort after 15 artificial knee joints and eight knees with more than 5° flexion contracture were omitted. The study was conducted with approval of the Institutional Review Boards (IRBs) of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology, and all participants provided written informed consent.

RADIOGRAPHY

Plain radiographs with standing on both legs and the knee extended were taken with a horizontal X-ray beam unless otherwise described, using a Fuji 5000 Plus Reader on a 36 × 46 cm Fuji ST-VI Computed Radiography (CR) imaging plate (Fuji Medical Systems, Tokyo, Japan) with a 20 × 30 mm rectangular metal plate beside it as a magnification index. Rotation of the foot was adjusted to keep the second metatarsal bone parallel to the X-ray beam. Images were downloaded into Digital Imaging and Communication in Medicine (DICOM) format files with a spatial resolution of 1584 × 2016 pixels (giving a pixel size of 0.01 mm) and 1024 gray levels.

IMAGE PROCESSING BY KOACAD

The KOACAD was programmed to perform the following operations automatically on the digital images above using the object-oriented programming language C++ [Fig. 1(A)]. Initially, correction for radiographic magnification was performed based on the image size of the rectangular metal plate. To reduce the image noise, the entire radiograph underwent filtering three times with a 3 × 3 square neighborhood median filter as reported previously[21]. Then, the Robert's filter was applied to extract the rough outlines of tibia and femur, so that medial and lateral sides could be judged by the difference of calculated widths of tibia and fibula at the level of 100 pixels above the bottom of the image [Fig. 1(B)].

Next, to determine the region of interest (ROI) including the tibiofemoral joint space, a vertical neighborhood difference filter was applied to identify points with high absolute values of difference of scales. The center of all the points was then calculated, and 480 × 200 pixels of a rectangle with the center was decided as the ROI [Fig. 1(C)]. Within the ROI, the outline of femoral condyle was designated as the upper rim of the joint space by vertical filtering with the 3 × 3 square neighborhood difference filter [Fig. 1(D)]. The two ends were determined using a Canny's filter to remove the noise of lines[22], and vertical lines from the ends were designated as the outside rims of the joint space. Outlines of anterior and posterior margins of the tibial plateau were drawn similarly to that of the femoral condyle, and the middle line between the two outlines was designated as the lower rim of the joint space [Fig. 1(E)]. Then, a straight regression line for the lower rim outline was drawn, and their intersections were designated as the inside rims [Fig. 1(F)]. The medial and lateral JSAs were determined as the areas surrounded by the upper, lower, inside, and outside rims above [Fig. 1(G)]. The medial and lateral mJSWs were further determined as the minimum vertical distances in the respective JSA [Fig. 1(H)].

To measure osteophyte area and TFA, the medial and lateral outlines of femur and tibia were drawn by the 3 × 3 square horizontal neighborhood difference filter and Canny's filter as described above. Then, the inflection points for the outlines were calculated. The medial outline of the tibia from the inflection point was drawn upward to the joint level [Fig. 1(I)], and the area that was medially prominent over the smoothly extended outline was designated as the osteophyte area [Fig. 1(J)]. For TFA, a middle line between the medial and lateral outlines of the femur from the top of the image to the inflection points was drawn [Fig. 1(K)], and the straight regression line was determined to be the axis of the femur. Similarly, the straight regression line of the middle line of the tibia from the bottom to the inflection points was designated as the axis of the tibia. The lateral angle between the two axis lines was calculated as TFA [Fig. 1(L)].

ANALYSES

To decide the ideal conditions for the taking of radiographs for the KOACAD analysis, we initially evaluated the reproducibility of the six parameters by an intraclass coefficient of correlation (ICC) on radiographs of 20 individuals taken at a 2-week interval with various knee flexion angles (0, 10, 20, and 30°) and X-ray beam angulations (0, 5, 10, and 15°).

Conventional gradings by the K/L system and the OARSI radiographic atlas were performed by experienced orthopedists on 50 radiographs randomly selected from the 1979 radiographs above, and intra- and interobserver variabilities were evaluated by κ values. The KOACAD parameters were also evaluated by semi-automatic measurement by a conventional computer-assisted program (Quick Grain Standard, Inotech, Hiroshima, Japan) after drawing of the outlines of femur and tibia by the orthopedists, and intra- and interobserver ICCs of each parameter were compared with those of KOACAD.

Correlations of the KOACAD parameters with the K/L grading (0–4) were examined by Spearman's correlation test on the entire 1979 radiographs. Correlations with the OARSI grading (0–3) were similarly examined for five common parameters: the KOACAD mJSW and JSA at the medial and lateral sides were compared with the OARSI joint space narrowing grades at the respective sides, and the KOACAD osteophyte area with the OARSI osteophyte grade of the medial tibial plateau. Since there was no radiograph of OARSI grade 3 of lateral joint space narrowing, correlations of the KOACAD lateral JSA and lateral mJSW were examined with the OARSI grade 0–2.

Correlations among the KOACAD parameters were analyzed using Pearson's correlation test, and parameters with correlation value of more than 0.5 were defined as confounding factors.

For the assessment of factors associated with symptomatic knee pain, age and the six KOACAD parameters were compared between knees with and without pain by Student's *t* test on the 1979 radiographs. Logistic regression analyses were used to estimate odds ratio (OR) and the associated 95% confidence interval (CI). Final multivariate logistic models were created through stepwise elimination of variables of interest from univariate analysis after adjustment for age and confounding factors.

A *P*-value of <0.05 for analysis of safety variables was considered significant. Data analyses were performed using SAS version 9.0 (SAS Institute Inc., NC, USA).

Results

REPRODUCIBILITY OF KOACAD PARAMETERS BY KNEE FLEXION ANGLES AND X-RAY BEAM ANGULATIONS

The KOACAD system could automatically measure the six parameters on an anteroposterior knee radiograph in

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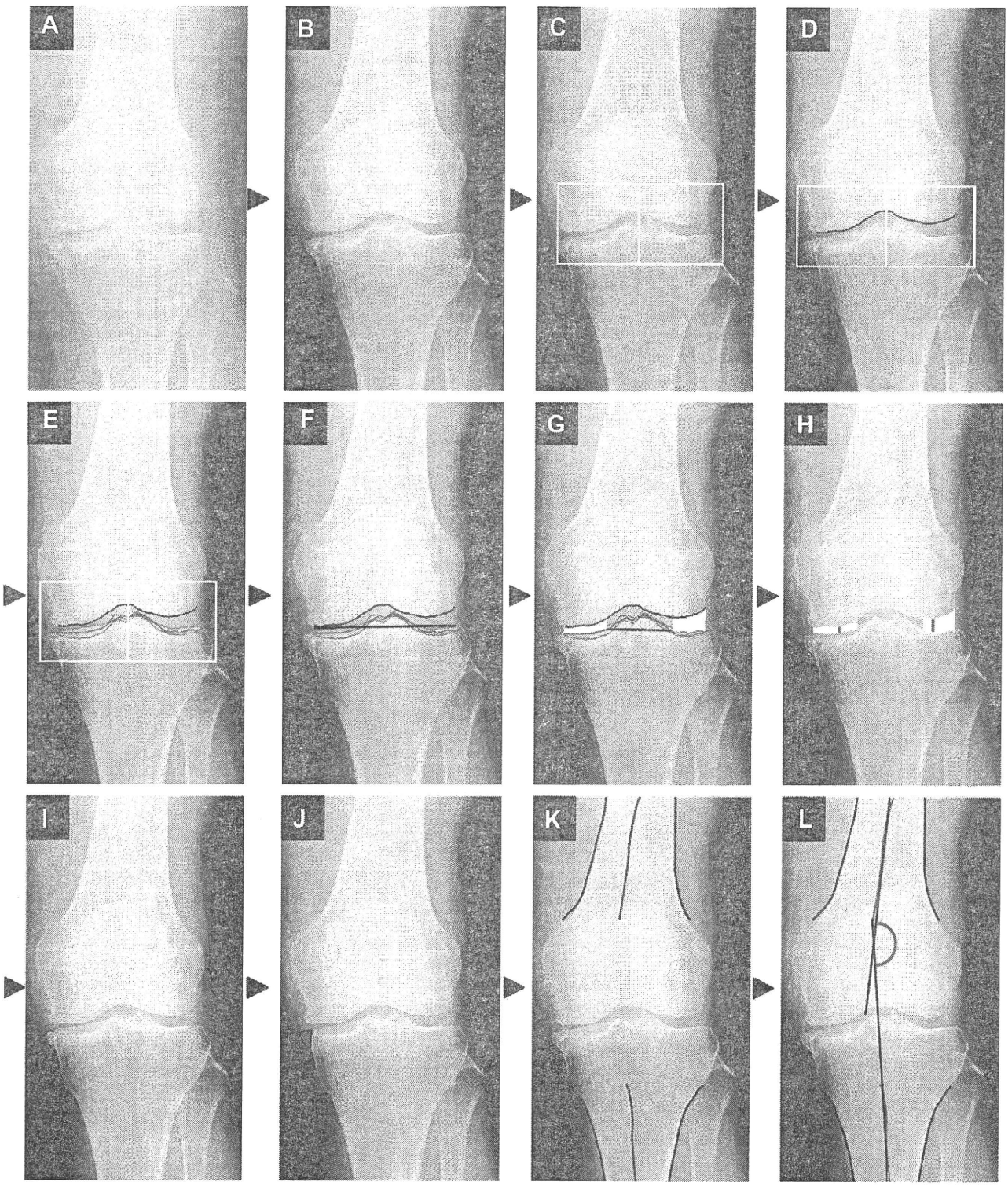

Fig. 1. Schema of image processing by KOACAD. (A) A digitized knee radiograph as a DICOM file. (B) Filterings to reduce the image noise and to extract outlines of tibia and femur. (C) ROI and the center including the tibiofemoral joint space. (D) An outline of femoral condyle (blue line) as the upper and outside rims of the joint space. (E) Outlines of anterior and posterior margins of the tibial plateau (green lines), and the middle line between the two outlines (red line) as the lower rim of the joint space. (F) A straight regression line (black line) for the lower rim line, and their intersections as the inside rims. (G) Medial and lateral JSAs (white areas) surrounded by the upper, lower, inside, and outside rims. (H) Medial and lateral mJSWs (brown lines) as the minimum vertical distances in the JSAs. (I) Medial outline (blue line) of the tibia drawn from the calculated inflection point upward to the joint level. (J) Osteophyte area (red area) that is medially prominent over the smoothly extended outline of the tibia. (K) Medial and lateral outlines (blue lines) of the femur and tibia from the edges of the image to the inflection points, and the middle lines (purple lines). (L) TFA as the lateral angle between the straight regression lines (black lines) of the middle lines above in the femur and tibia.

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less than 1 s without any manual operation. To decide the ideal conditions of taking radiographs for the KOACAD analysis, we first examined the reproducibility of the parameters measured on radiographs of 20 individuals taken at a 2-week interval with various knee flexion angles and X-ray beam angulations (Table I). The reproducibility of all parameters was highly maintained with 0° of the knee flexion angle (ICC = 0.88–0.99), which became lower as the angle was increased. It was also maintained with 0 and 5° of X-ray beam angulations (ICC = 0.87–0.99), while it was not determined in most of the radiographs with 10 and 15° due to overlap of femoral condyle and tibial plateau. Hence, we decided to take radiographs with the knee extended and a horizontal X-ray beam for the KOACAD measurement.

COMPARISON OF KOACAD WITH CONVENTIONAL SYSTEMS

We measured the six parameters by KOACAD more than twice on 1979 radiographs, and confirmed that all parameters were unchanged independent of observer or time measured (all ICC = 1.0). Contrarily, when we examined the intra- and interobserver variabilities of the conventional categorical grading systems on 50 randomly selected radiographs, the intra- and interobserver variabilities were high by the K/L system (κ value = 0.84 and 0.76) and the OARSI radiographic atlas ($\kappa \leq 0.75$ and ≤ 0.65) (Supplementary Table S1). In addition, the intra- and interobserver ICCs of semi-automatic measurements using a conventional computer-assisted procedure of the parameters were less than 0.7 and 0.6, respectively, for joint space parameters and osteophyte area, and were less than 0.8 for TFA, indicating that even this computer-assisted system is robust with respect to variability in lines drawn by observers for the computer to analyze (Supplementary Table S1).

We then examined the correlations of the KOACAD parameters with the K/L and OARSI gradings on the 1979 radiographs (Table II). All parameters were significantly correlated with the K/L grading ($P < 0.0001$); with medial JSA, medial mJSW, and TFA being most strongly correlated with it. Five common parameters showed good correlation between KOACAD and OARSI grading ($P < 0.0001$), and medial JSA and medial mJSW also showed most of the strong correlations.

CORRELATIONS AMONG THE KOACAD PARAMETERS

Although all KOACAD parameters are known to be affected as OA progresses, the changes are neither proportional nor is the relationship constant. We therefore examined the correlations among the parameters on the 1979 radiographs by Pearson's correlation test (Table III). As expected, correlation values were more than 0.5 between medial JSA and medial mJSW, and between lateral JSA and lateral mJSW, indicating that these are confounding factors for each other. More interestingly, although osteophyte area was measured at the medial tibia, it was significantly associated with neither medial JSA nor mJSW, suggesting different etiologic mechanisms between osteophyte formation and joint destruction. Furthermore, JSA and mJSW at the lateral side were positively correlated with those at the medial side, and TFA was strongly associated with decreased mJSWs not only at the medial side but also at the lateral side. This implies that there is a background generally affecting the whole joint for OA progression rather than the medial-lateral shift of loading axis of mechanical stress within the joint.

CORRELATIONS OF THE KOACAD PARAMETERS WITH KNEE PAIN

To further identify radiographic factors associated with knee pain using the KOACAD system in the 1979 radiographs, we compared the parameters between groups with (594 knees) and without (1385 knees) knee pain (Table IV). Although age was comparable, all parameters were significantly different between the two groups. Especially, medial JSA and medial mJSW were lower and TFA was higher in the group with pain than that without pain. Univariate logistic regression analysis after adjustment for age revealed that female sex (OR = 1.64; 95% CI = 1.47–1.84), medial JSA (1.16; 1.05–1.27), medial mJSW (1.66; 1.49–1.87), and TFA (1.07; 1.03–1.10) were significantly associated with the presence of pain.

Considering that medial mJSW and medial JSA, as well as lateral mJSW and lateral JSA, were found to be confounders for each other (Pearson's correlation value > 0.5; Table III), we performed a multivariate analysis after adjustment for age and confounding factors in both genders

Table I

Reproducibility of KOACAD parameters measured on radiographs of an individual with various knee flexion angles and X-ray beam angulations

Knee flexion angle (°)	0	10	20	30
KOACAD parameters (ICC)				
Medial JSA (mm^2)	0.88	0.77	0.74	0.74
Lateral JSA (mm^2)	0.92	0.87	0.73	0.73
Medial mJSW (mm)	0.96	0.92	0.90	0.78
Lateral mJSW (mm)	0.95	0.86	0.88	0.80
Osteophyte area (mm^2)	0.99	0.91	0.79	0.81
TFA (°)	0.94	0.93	0.86	0.86
X-ray beam angulation (°)	0	5	10	15
KOACAD parameters (ICC)				
Medial JSA (mm^2)	0.88	0.87	ND	ND
Lateral JSA (mm^2)	0.92	0.92	(17/20)	(20/20)
Medial mJSW (mm)	0.96	0.96		
Lateral mJSW (mm)	0.95	0.95		
Osteophyte area (mm^2)	0.99	0.99		
TFA (°)	0.94	0.93		

Reproducibility of six parameters was evaluated by an ICC on radiographs of 20 individuals taken at a 2-week interval. ND: not determined due to overlap of femur and tibia.

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Table II
Correlations of the KOACAD parameters with the K/L and OARSI gradings

	0	1	2	3	4	R^2
K/L grading						
Number	162	625	956	205	31	
Medial JSA (mm^2)	112.4 ± 1.8	97.0 ± 0.9	91.1 ± 0.7	83.2 ± 1.9	52.4 ± 5.4	−0.29
Lateral JSA (mm^2)	114.3 ± 2.0	110.6 ± 1.1	107.2 ± 0.9	105.3 ± 1.9	106.2 ± 6.1	−0.09
Medial mJSW (mm)	3.9 ± 0.1	3.4 ± 0.0	3.1 ± 0.0	2.5 ± 0.1	1.5 ± 0.2	−0.41
Lateral mJSW (mm)	4.7 ± 0.1	4.4 ± 0.0	4.3 ± 0.1	4.2 ± 0.1	4.2 ± 0.3	−0.11
Osteophyte area (mm^2)	2.7 ± 1.4	2.0 ± 0.2	3.2 ± 0.2	7.9 ± 1.3	10.9 ± 4.2	0.15
TFA (°)	175.7 ± 0.2	176.2 ± 0.1	177.4 ± 0.1	179.6 ± 0.3	184.2 ± 1.2	0.31
OARSI grading						
Medial JSA (mm^2) (n)	105.9 ± 0.9 (602)	89.8 ± 0.7 (953)	90.0 ± 1.3 (317)	65.4 ± 2.2 (107)		−0.34
Lateral JSA (mm^2) (n)	109.6 ± 0.6 (1926)	87.7 ± 4.2 (38)	61.7 ± 7.3 (15)	− (0)		−0.16
Medial mJSW (mm) (n)	3.6 ± 0.0 (602)	3.1 ± 0.0 (953)	2.7 ± 0.0 (317)	1.8 ± 0.1 (107)		−0.45
Lateral mJSW (mm) (n)	4.3 ± 0.0 (1926)	3.3 ± 0.2 (38)	2.5 ± 0.3 (15)	− (0)		−0.19
Osteophyte area (mm^2) (n)	2.0 ± 0.2 (1212)	2.8 ± 0.4 (421)	4.7 ± 0.6 (215)	14.7 ± 0.7 (131)		0.25

Analyses were performed by Spearman's correlation test on 1979 radiographs, and data are expressed by means ± S.E.M. (all *P*-values < 0.0001).

(Table V). It was found that low medial mJSW and high TFA were associated with the presence of pain, while neither lateral mJSW nor osteophyte area was.

Discussion

In the present study, we established a fully automatic computer-assisted program, KOACAD that can quantitate the major features of knee OA on plain radiographs. This system has achieved objective, accurate, simple and easy assessment of the structural severity of knee OA without any manual operation in general clinical practice or in population-based epidemiologic studies. The system could also accurately evaluate distinct features of knee OA like joint space narrowing, osteophyte formation, and joint angulation in one sitting. By applying this system to the baseline data in the ROAD study, medial joint space narrowing and varus angulation, though neither lateral joint space narrowing nor osteophyte formation, was shown to be associated with symptomatic knee pain.

Independent measurement of the parameters by KOACAD enabled us to examine the correlation of distinct features of OA, which may lead to better understanding of the OA pathophysiology. For example, a lack of association between osteophyte formation and joint space narrowing indicates independent backgrounds of the two representative features of knee OA. A previous prospective study using a famous OA cohort, the Chingford study, has reported that there was no association between the two features[23]. Although the authors described in the paper that this might possibly be due to inaccurate and subjective measurement on radiographs, the present KOACAD analysis has confirmed the reliability by accurate and objective measurement. A recent cross-sectional study has also shown that osteophyte formation was unrelated not only to joint space narrowing on plain radiographs, but also to cartilage loss measured by quantitative MRI[24]. Furthermore, by creating an OA model through induction of instability in mouse knee joints, we have identified a cartilage specific molecule, carminerin, that regulates osteophyte formation without affecting cartilage destruction during the OA progression[25,26]. Further clinical and basic research will disclose the distinct backgrounds of the two OA features. The correlation analysis among the parameters also revealed that joint space narrowing at medial and lateral sides was positively correlated, indicating an etiologic mechanism that affects the whole joint. Although this does not necessarily deny the mechanistic contribution of medial-lateral shift of the loading axis within the joint to the OA progression, the limitation of efficacy of a valgus knee brace, lateral wedged insole, or valgus high tibial osteotomy for medial compartment OA of the knee may at least partly be explained by the result.

For accurate and reproducible assessment of tibiofemoral joint space on plain radiographs, a variety of radiographic methods have been developed. Several reports have claimed that positioning of the knee with several angles of flexion provides more accurate joint space measurement than conventional extended knees due to superimposition of the anterior and posterior margins of the tibial plateau[13,27,28]. Among the reports, angulation of the X-ray beam and rotation of the foot were different, and some of them included fluoroscopic assistance for the adjustment of margins of the tibial plateau. Despite these efforts, none of the radiographic protocols has realized high reproducibility or sensitivity for long-term longitudinal

Table III
Correlations among the KOACAD parameters

	Medial JSA	Lateral JSA	Medial mJSW	Lateral mJSW	Osteopyte area	TFA
Medial JSA	1.00					
Lateral JSA	0.22 (<0.0001)	1.00				
Medial mJSW	0.70 (<0.0001)	0.13 (0.0008)	1.00			
Lateral mJSW	0.18 (<0.0001)	0.72 (<0.0001)	0.22 (<0.0001)	1.00		
Osteophyte area	0.02 (NS)	−0.13 (0.0006)	0.04 (NS)	−0.13 (NS)	1.00	
TFA	−0.08 (0.03)	0.03 (NS)	−0.21 (<0.0001)	−0.19 (<0.0001)	−0.02 (NS)	1.00

Analyses were performed by Pearson's correlation test on 1979 radiographs, and data are expressed as Pearson's correlation values and *P*-values in the parentheses. NS: not significant ($P > 0.05$).

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Table IV
Differences of age and the KOACAD parameters between knees with and without pain

	Pain (+)	Pain (−)	*P*-value
Participants (men/women)	594 (124/470)	1385 (575/810)	
Age (years)	76.8 ± 4.7	77.0 ± 4.4	NS
Parameters			
Medial JSA (mm^2)	88.0 ± 1.0	95.7 ± 0.7	<0.0001
Lateral JSA (mm^2)	105.9 ± 1.1	110.2 ± 0.7	0.0013
Medial mJSW (mm)	2.9 ± 1.0	3.3 ± 1.2	<0.0001
Lateral mJSW (mm)	4.3 ± 0.1	4.4 ± 0.0	0.0044
Osteophyte area (mm^2)	4.8 ± 5.4	2.9 ± 7.0	0.0002
TFA (°)	177.9 ± 3.3	176.9 ± 4.3	<0.0001

Analyses were performed on 1979 radiographs, and data are expressed by means ± S.E.M. *P*-values were determined by Student's *t* test. NS: not significant ($P > 0.05$).

studies[27,29]. And, first of all, since these methods increase the cost and require the technician to be specifically trained, they are unlikely to be applicable in general clinical practice or population-based epidemiologic studies. Meanwhile, the conventional standing extended view knee radiographs that the KOACAD system adopted are known to be sensitive to change if the tibial plateau is adequately aligned[30]. To overcome variability of the tibiofemoral joint space by the positioning of the knee and the angulation of the X-ray beam causing the misalignment of the anterior and posterior margins of the tibial plateau, the KOACAD system for the first time designated the middle line between outlines of anterior and posterior margins of the tibial plateau as the lower rim of the radiographic joint space. In fact, reproducibility of all KOACAD parameters was highly maintained with 0° knee flexion and 0–5° X-ray angulation (Table I). This, however, indicates that OA patients with flexion contracture of the knee cannot be appropriately assessed by the KOACAD system, so that patients with more than 5° flexion contracture were excluded from the present study.

Digital images by computed radiographic techniques offer several advantages compared with conventional analog film-screen radiography, and are increasingly available in routine patient management because they allow image enhancement, quantification, archiving, transmission, simultaneous access to the image at multiple sites, and reduction in radiation dose[31]. Although this study used digitized images as the DICOM file, we have confirmed that images digitized from analog radiographs by general image scanners could be used for the KOACAD analysis with perfect reproducibility (ICC = 1.0). In addition, since KOACAD is programmed based on a personal computer, and not on a massive workstation, it can be used anywhere, even away from clinics.

Table V
Multivariate logistic regression analysis for OR and 95% CI of the KOACAD parameters for knee pain

	Men (699)		Women (1280)	
	OR	95% CI	OR	95% CI
Medial mJSW	1.46	1.16–1.90	1.41	1.23–1.63
Lateral mJSW	0.99	0.79–1.23	1.10	0.98–1.24
Osteophyte area	0.99	0.96–1.04	0.99	0.98–1.00
TFA	1.07	1.01–1.13	1.07	1.03–1.10

Data were calculated by stepwise logistic regression analysis after adjustment for age and confounding factors on 1979 radiographs.

The relationship between the radiographic findings and the symptomatic pain in knee joints remains controversial, but at least the severity of radiographic OA is not linearly correlated with that of pain[18–20]. Although the present multivariate analysis was able to detect significant associations of knee pain with low medial mJSW and high TFA, they were not strong (Table V). This may be due to the complicated mechanism underlying the pain. Although articular cartilage is viewed as a major target tissue of OA, knee pain may arise from a number of different structures like joint capsule, ligaments, menisci, bursae, and the bone marrow. Pathological structures caused by OA may contribute to pain indirectly. For example, inflammatory synovitis and associated capillaries are innervated by pain fibers and may be affected in OA[32]. Furthermore, previous MRI surveys among patients with radiographic knee OA showed that knee pain was due not only to OA-related disorders, but also to spontaneous osteonecrosis and bone marrow edema around the knee joint[33–35]. A limitation of the KOACAD system is that these periarticular disorders are not included in the parameters but are best shown by MRI, which might possibly lead to failures in the treatment of knee pain.

Another limitation of this study is a lack of longitudinal investigation to validate the sensitivity of the KOACAD system. One criticism has been that plain radiographs are insensitive to change over time, and that even a small radiographic change is associated with substantial cartilage loss[36]. Nevertheless, the current recommendations suggest that clinical studies of knee OA should include a structural measure of OA severity[5,28]. This emphasizes the need for further refinement in the definition of radiographic outcomes in prospective clinical trials. Recent longitudinal studies using quantitative MRI have shown that subjects with knee OA lose 5% of their tibial cartilage volume per year[37,38] and that the cartilage loss is correlated with worsening of symptoms and portends knee replacement[20,39]. Although the cartilage loss detected by quantitative MRI is much greater than that detected in plain radiographs, the MRI-based cartilage volume correlates with the change of radiographic features to some extent[40,41]. Since the KOACAD system can provide continuous measures of parameters of OA severity, it is possible that the system is as sensitive to change over time as quantitative MRI. Also, the association between knee pain and radiographic features cannot be appropriately assessed in a cross-sectional survey, but should be evaluated over a defined period of time, as indicated by previous reports[42,43]. Our baseline survey in the ROAD study has included quantitative MRI on a group of randomly selected participants. In 2008–2010, we are planning a second survey including the KOACAD radiographic analysis on more than 3000 participants and the quantitative MRI on a portion of these. Comparison of the KOACAD parameters and the MRI findings will validate the sensitivity of the KOACAD system over time, and lead to further understanding of the association between knee pain and radiographic features.

In conclusion, we have established a fully automatic computer-assisted program, KOACAD, to quantify knee OA severity on plain radiographs, and validated its high reproducibility and reliability in a cross-sectional study. This system may not only be useful for objective evaluation of knee OA patients in daily clinical practice or in population-based epidemiologic studies, but also act as a proper surrogate measure for the development of disease-modifying drugs for OA. We hope in the future that this system will be prevalently used worldwide to lead to international criteria for diagnosis and treatment of knee OA, just like BMD in osteoporosis.

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Conflict of interest

There are no conflicts of interest.

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Supplementary material

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References

1. Sharma L, Kapoor D. Epidemiology of osteoarthritis. In: Moskowitz RW, Altman RD, Hochberg MC, Buckwalter JA, Goldberg VM, Eds. Osteoarthritis: Diagnosis and Medical/Surgical Management. 4th edn. Philadelphia: Lippincott Williams & Wilkins; 2007:3–26.
2. Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW, *et al.* The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health 1994;84:351–8.
3. Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. Arthritis Rheum 1998;41:1343–55.
4. Yelin E, Callahan LF. The economic cost and social and psychological impact of musculoskeletal conditions. National Arthritis Data Work Groups. Arthritis Rheum 1995;38:1351–62.
5. Abadie E, Ethgen D, Avouac B, Bouvenot G, Branco J, Bruyere O, *et al.* Recommendations for the use of new methods to assess the efficacy of disease-modifying drugs in the treatment of osteoarthritis. Osteoarthritis Cartilage 2004;12:263–8.
6. Burstein D, Gray ML. Is MRI fulfilling its promise for molecular imaging of cartilage in arthritis? Osteoarthritis Cartilage 2006;14:1087–90.
7. Eckstein F, Burstein D, Link TM. Quantitative MRI of cartilage and bone: degenerative changes in osteoarthritis. NMR Biomed 2006;19:822–54.
8. Bauer DC, Hunter DJ, Abramson SB, Attur M, Corr M, Felson D, *et al.* Classification of osteoarthritis biomarkers: a proposed approach. Osteoarthritis Cartilage 2006;14:723–7.
9. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.
10. Altman RD, Hochberg M, Murphy WA Jr, Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. Osteoarthritis Cartilage 1995;3(Suppl A):3–70.
11. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage 2007;15(Suppl A):A1–A56.
12. Dacre JE, Huskisson EC. The automatic assessment of knee radiographs in osteoarthritis using digital image analysis. Br J Rheumatol 1989;28:506–10.
13. Buckland-Wright JC, Macfarlane DG, Williams SA, Ward RJ. Accuracy and precision of joint space width measurements in standard and macroradiographs of osteoarthritic knees. Ann Rheum Dis 1995;54:872–80.
14. Prakash U, Wigderowitz CA, McGurty DW, Rowley DI. Computerised measurement of tibiofemoral alignment. J Bone Joint Surg Br 2001; 83:819–24.
15. Bruyere O, Henrotin YE, Honore A, Rovati LC, Seidel L, Dardenne C, *et al.* Impact of the joint space width measurement method on the design of knee osteoarthritis studies. Aging Clin Exp Res 2003;15:136–41.
16. Takahashi T, Yamanaka N, Komatsu M, Ogawa Y, Yoshida S, Yamamoto H. A new computer-assisted method for measuring the tibio-femoral angle in patients with osteoarthritis of the knee. Osteoarthritis Cartilage 2004;12:256–9.
17. Linaker CH, Walker-Bone K, Palmer K, Cooper C. Frequency and impact of regional musculoskeletal disorders. Baillieres Clin Rheumatol 1999;13:197–215.
18. Summers MN, Haley WE, Reveille JD, Alarcon GS. Radiographic assessment and psychologic variables as predictors of pain and functional impairment in osteoarthritis of the knee or hip. Arthritis Rheum 1988;31:204–9.
19. Cicuttini FM, Baker J, Hart DJ, Spector TD. Association of pain with radiological changes in different compartments and views of the knee joint. Osteoarthritis Cartilage 1996;4:143–7.
20. Wluka AE, Wolfe R, Stuckey S, Cicuttini FM. How does tibial cartilage volume relate to symptoms in subjects with knee osteoarthritis? Ann Rheum Dis 2004;63:264–8.
21. Boyle RD, Thomas RC. Median filter. In: Boyle RD, Thomas RC, Eds. Computer Vision: a First Course. Blackwell Scientific Publications 1988:32–4.
22. Canny J. A computational approach to edge detection. IEEE Trans Pattern Anal Mach Intell 1986;8:679–714.
23. Hart DJ, Doyle DV, Spector TD. Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women: the Chingford Study. Arthritis Rheum 1999;42:17–24.
24. Jones G, Ding C, Scott F, Glisson M, Cicuttini F. Early radiographic osteoarthritis is associated with substantial changes in cartilage volume and tibial bone surface area in both males and females. Osteoarthritis Cartilage 2004;12:169–74.
25. Kamekura S, Kawasaki Y, Hoshi K, Shimoaka T, Chikuda H. Contribution of runt-related transcription factor 2 to the pathogenesis of osteoarthritis in mice after induction of knee joint instability. Arthritis Rheum 2006;54:2462–70.
26. Yamada T, Kawano H, Koshizuka Y, Fukuda T, Yoshimura K, Kamekura S, *et al.* Carminerin contributes to chondrocyte calcification during endochondral ossification. Nat Med 2006;12:665–70.
27. Brandt KD, Mazzuca SA, Conrozier T, Dacre JE, Peterfy CG, Provvedini D, *et al.* Which is the best radiographic protocol for a clinical trial of a structure modifying drug in patients with knee osteoarthritis? J Rheumatol 2002;29:1308–20.
28. Strand V, Hochberg MC. Study design and outcome measures in osteoarthritis clinical trials. In: Moskowitz RW, Altman RD, Hochberg MC, Buckwalter JA, Goldberg VM, Eds. Osteoarthritis: Diagnosis and Medical/Surgical Management. 4th edn. Philadelphia: Lippincott Williams & Wilkins; 2007:313–25.
29. Mazzuca SA, Brandt KD, Buckwalter KA. Detection of radiographic joint space narrowing in subjects with knee osteoarthritis: longitudinal comparison of the metatarsophalangeal and semiflexed anteroposterior views. Arthritis Rheum 2003;48:385–90.
30. Mazzuca SA, Brandt KD, Dieppe PA, Doherty M, Katz BP, Lane KA. Effect of alignment of the medial tibial plateau and x-ray beam on apparent progression of osteoarthritis in the standing anteroposterior knee radiograph. Arthritis Rheum 2001;44:1786–94.
31. Sanfridsson J, Holje G, Svahn G, Ryd L, Jonsson K. Radiation dose and image information in computed radiography. A phantom study of angle measurements in the weight-bearing knee. Acta Radiol 2000; 41:310–6.
32. Saito T, Koshino T. Distribution of neuropeptides in synovium of the knee with osteoarthritis. Clin Orthop Relat Res 2000;376:172–82.
33. Karachalios T, Zibis A, Papanagiotou P, Karantanas AH, Malizos KN, Roidis N. MR imaging findings in early osteoarthritis of the knee. Eur J Radiol 2004;50:225–30.
34. Felson DT, Chaisson CE, Hill CL, Totterman SM, Gale ME, Skinner KM, *et al.* The association of bone marrow lesions with pain in knee osteoarthritis. Ann Intern Med 2001;134:541–9.
35. Bollet AJ. Edema of the bone marrow can cause pain in osteoarthritis and other diseases of bone and joints. Ann Intern Med 2001;134:591–3.
36. Ravaud P, Giraudeau B, Auleley GR, Drape JL, Rousselin B, Paolozzi L, *et al.* Variability in knee radiographing: implication for definition of radiological progression in medial knee osteoarthritis. Ann Rheum Dis 1998;57:624–9.
37. Wluka AE, Stuckey S, Snaddon J, Cicuttini FM. The determinants of change in tibial cartilage volume in osteoarthritic knees. Arthritis Rheum 2002;46:2065–72.
38. Burgkart R, Glaser C, Hinterwimmer S, Hudelmaier M, Englmeier KH, Reiser M, *et al.* Feasibility of T and Z scores from magnetic resonance imaging data for quantification of cartilage loss in osteoarthritis. Arthritis Rheum 2003;48:2829–35.
39. Cicuttini FM, Jones G, Forbes A, Wluka AE. Rate of cartilage loss at two years predicts subsequent total knee arthroplasty: a prospective study. Ann Rheum Dis 2004;63:1124–7.
40. Raynauld JP, Martel-Pelletier J, Berthiaume MJ, Labonte F, Beaudoin G, de Guise JA, *et al.* Quantitative magnetic resonance imaging evaluation of knee osteoarthritis progression over two years and correlation with clinical symptoms and radiologic changes. Arthritis Rheum 2004;50:476–87.
41. Cicuttini F, Hankin J, Jones G, Wluka A. Comparison of conventional standing knee radiographs and magnetic resonance imaging in assessing progression of tibiofemoral joint osteoarthritis. Osteoarthritis Cartilage 2005;13:722–7.
42. Ledingham J, Regan M, Jones A, Doherty M. Factors affecting radiographic progression of knee osteoarthritis. Ann Rheum Dis 1995;54: 53–8.
43. van Dijk GM, Dekker J, Veenhof C, van den Ende CH. Course of functional status and pain in osteoarthritis of the hip or knee: a systematic review of the literature. Arthritis Rheum 2006;55:779–85.

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Prevalence of radiographic lumbar spondylosis and its association with low back pain in the elderly of population-based cohorts: the ROAD study

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Prevalence of radiographic lumbar spondylosis and its association with low back pain in the elderly of population-based cohorts: the ROAD study

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Running title: Prevalence of radiographic lumbar spondylosis and association with pain

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ABSTRACT

Objectives: Although lumbar spondylosis is a major cause of low back pain and disability in the elderly, few epidemiologic studies have been performed. We investigated the prevalence of radiographic lumbar spondylosis using a large-scale population, and examined the association with low back pain.

Methods: From a nationwide cohort study ROAD (Research on Osteoarthritis Against Disability), 2,288 participants (≥60 years; 818 men and 1,470 women) living in urban, mountainous and seacoast communities were analyzed. The radiographic severity at lumbar intervertebral levels from L1/2 to L5/S was determined by the Kellgren/Lawrence (KL) grading.

Results: In the overall population, prevalence of radiographic spondylosis with KL≥2 and ≥3 at the severest intervertebral level was 75.8 and 50.4%, respectively, and that of low back pain was 28.8%. Although the KL≥2 spondylosis was more prevalent in men, the KL≥2 spondylosis and low back pain were more prevalent in women. Age and body mass index were risk factors for both KL≥2 and KL≥3 spondylosis. Although KL=2 spondylosis was not significantly associated with low back pain compared to KL=0 or 1, KL≥3 spondylosis was related to the pain only in women.

Conclusions: The present cross-sectional study using a large population revealed a high prevalence of radiographic lumbar spondylosis in the elderly. Gender seems to be distinctly associated with KL≥2 and KL≥3 lumbar spondylosis, and disc space narrowing with or without osteophytosis in women may be a risk factor for low back pain.

Key words: Osteoarthritis, spondylosis, lumbar spine, prevalence, pain

INTRODUCTION

Lumbar spondylosis is considered a major public health issue causing chronic disability of the elderly in most developed countries (1,2). Despite the urgent need for strategies for the prevention and treatment of this condition, the epidemiologic data on lumbar spondylosis such as its prevalence and association with symptoms are sparse. With the goal of establishing epidemiologic indexes to evaluate clinical evidence for the development of the disease-modifying treatment, we set up a large-scale nationwide cohort study for bone and joint disease called ROAD (Research on Osteoarthritis Against Disability) in 2005. We have to date created a baseline database with detailed clinical and genetic information on three population-based cohorts in urban, mountainous and seacoast communities of Japan.

Lumbar spondylosis is characterized by disc degeneration and osteophytosis (2,3). Although this disorder has been widely studied in a clinical setting, few population-based radiologic studies have been attempted (4-11). The reported prevalence of radiographic lumbar spondylosis differs greatly in these reports from about 40 to 85%. This may be due to limitation of the sample size and variability of age. Hence, the present study initially investigated the prevalence and distribution of this disorder according to age, gender and community using cohorts of 2,288 participants 60 years or older in the baseline survey of the ROAD study.

The most popular grading system for the radiographic severity of osteoarthritis is the Kellgren / Lawrence (KL) system with classification into five-grade (0-4) scales, and KL≥2 is the conventional standard of the diagnosis (12). For lumbar spondylosis, KL grade 2 is defined as osteophyte formation and grade 3 as disc space narrowing in addition to osteophyte formation (12), although there are few epidemiologic studies which have applied the KL system to evaluate the lumbar spine (5, 6, 9). Hence, to assess osteophyte formation alone and disc space narrowing with or without osteophytosis separately, the present study examined not only the prevalence of KL≥2 spondylosis but also that of KL≥3 spondylosis.

Although low back pain is believed to be the principal clinical symptom of lumbar spondylosis, its association with the radiographic severity remains unclarified. The correlation was not as strong as one would expect, and there is often a disconnect between them (7,8). In previous reports, radiographic spondylosis was determined at the severest intervertebral level, but it is possible that other levels with milder spondylotic change might give rise to low back pain. This study therefore assessed the radiographic severity at all intervertebral levels of the lumbar spine by the KL system, and examined the association between the radiographic severity and low back pain.

METHODS

Participants

The ROAD study is a nationwide prospective cohort study for bone and joint diseases constituted of population-based cohorts established in several communities in Japan. To date, we have completed creation of a baseline database including clinical and genomic information of 3,040 inhabitants (men 1,061, women 1,979) in the age range 23-95 years (mean 70.6) in three communities: an urban region in Itabashi, Tokyo, a mountainous region in Hidakagawa, Wakayama, and a seacoast region in Taiji, Wakayama. Participants in the urban region were recruited from those of a cohort study (13) in which the participants were randomly drawn from the Itabashi-ward residents register database and the response rate in the age groups of 60 years or older were 75.6%. Participants in the mountainous and seacoast regions were recruited from

listings of resident registration and the response rates in the age groups of 60 years or older were 68.4 and 29.3%, respectively. All participants provided written informed consent, and the study was conducted with approval of ethical committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology. Participants completed an interviewer-administered questionnaire of 400 items which included lifestyle information such as smoking habits, alcohol consumption, family history, past history, physical activity, reproductive variables, and health-related quality of life. Anthropometric measurements included height, weight, arm span, bilateral grip strength, and body mass index (BMI; weight [kg] / height [m^2]). Medical information was taken by well-experienced orthopaedic surgeons (S.M. and H.O.) on systemic, local and mental status including information of low back, knee, and hip pain, swelling and range of motion of the joints, and patellar and achilles tendon reflex. All participants were interviewed regarding low back pain by asking, "In the past month, have you had pain on most days lasting?", and those who answered yes were defined as having low back pain. Blood and urine samples were collected for biochemical and genetic examinations. Plain radiographs of lumbar spine, knee and hip were taken for all participants. Participants were confirmed to be comparable to the Japanese general population according to the national nutrition survey by the Ministry of Health, Labour and Welfare (Japan). Height was 162.5 and 149.7 cm in men and women, respectively, in the ROAD study vs. 162.6 and 149.9 cm in the Japanese general population. Weight was 61.3 and 51.8 kg vs. 61.6 and 53.8 kg. Percentage of population with a smoking habit was 26.4 and 3.2% vs. 29.4 and 4.0%. From the baseline data of the overall participants, the present study analyzed 2,288 (818 men and 1,470 women) who were 60 years or older.

Radiographic assessment

Plain radiographs of the lumbar spine were taken at anteroposterior and lateral position, and the images were downloaded into Digital Imaging and Communication in Medicine (DICOM) format files to assess radiographic spondylosis. We used contrast-adjusted images to detect osteophytes and intervertebral spaces when the original images were obscure. Osteophytes were analyzed at endplates. The severity of lumbar spondylosis was determined according to the KL grading (12) at each intervertebral level from L1/2 to L5/S by a single well-experienced orthopaedist (S.M.) who was masked to the patients' backgrounds. To evaluate the intraobserver variability of the KL grading, 100 randomly selected radiographs of the lumbar spine were scored by the same observer more than one month after the first reading. Furthermore, 100 other radiographs were scored by two experienced orthopaedic surgeons (S.M. & H.O.) using the same radiographic atlas for interobserver variability. The intra- and interobserver variabilities were evaluated by the kappa analysis. These variabilities of the KL grading on lumbar radiographs have been shown to be sufficient for assessment (0.84 and 0.76, respectively).

Statistical analysis

The non-paired t-test was used to examine the difference of age and BMI between men and women. To compare the percentage of patients with radiographic spondylosis (KL grade$\geq$2 or $\geq$3 at the severest level) and low back pain between men and women, we performed a logistic regression analysis after adjustment for age and BMI. The differences of prevalence among the age-groups were determined using the one-way analysis of covariance and Scheffe's test after adjustment for BMI. The association of the variables such as age, BMI, gender and community

with the radiographic spondylosis and low back pain was evaluated by the multivariate logistic regression analysis. The association of radiographic spondylosis at each intervertebral level with low back pain was determined by the logistic regression analysis after adjustment for age and BMI. The association of the number of intervertebral level with KL≥3 with low back pain was determined by multiple regression analysis after adjustment for age and BMI. Data analyses were performed using SAS version 9.0 (SAS Institute Inc. NC).

RESULTS

Table 1 shows the overall characteristics of the 2,288 participants 60 years or older in the three cohorts of the ROAD study. Although men were significantly older than women in the overall population and in some communities, BMI was comparable between genders.

Table 2 shows the prevalence of radiographic lumbar spondylosis and low back pain in the overall population and subgroups classified by gender and age-strata. In the overall population, prevalence of radiographic spondylosis with KL≥2 and ≥3 at the severest intervertebral level was 75.8 and 50.4%, respectively, and that of low back pain was 28.8%. The prevalence of osteoporotic fracture at lumbar spine was 10.7 %. Logistic regression analysis after adjustment for age and BMI revealed that the prevalence of radiographic spondylosis with KL≥2 was higher in men than in women. Meanwhile, that of KL≥3 radiographic spondylosis and low back pain was higher in women than in men. When the prevalence was compared among the generations, radiographic spondylosis (KL≥2 and ≥3) and low back pain tended to increase with age. Interestingly, the difference was greater between <70 and 70-79 than between 70-79 and ≥80.

To identify risk factors for the radiographic spondylosis and low back pain, we further performed the logistic regression analysis to estimate odds ratios and confidence intervals (Table 3). Age and BMI were significantly associated with radiographic spondylosis. Male sex was confirmed to be a risk factor for KL≥2 spondylosis while female sex for KL≥ 3 and low back pain. Among the communities, mountainous area residents had a lower risk for KL≥3 spondylosis than urban residents.

We then examined the association between radiographic spondylosis and low back pain. Considering that intervertebral levels other than the severest level of radiographic spondylosis might possibly cause low back pain, the spondylosis at all intervertebral levels from L1/2 to L5/S was evaluated: KL≥2 spondylosis was found to be comparably prevalent at L2/3, L3/4 and L4/5, while KL≥3 spondylosis was remarkably prevalent at L4/5 in both men and women (Table 4). In fact, among the five levels L4/5 was most frequently determined to be the severest level in both genders (men: L1/2 49.4%, L2/3 59.5%, L3/4 58.0%, L4/5 64.5%, L5/S 48.3%, women: L1/2 49.5%, L2/3 58.0%, L3/4 58.6%, L4/5 65.5%, L5/S 44.3%). We then looked at the percentage of subjects with low back pain in three groups: KL=0 or 1, KL=2, and KL≥3, at each intervertebral level and the severest level in the overall population and the three communities (Figure 1). When odds ratios of KL=2 and KL≥3 spondylosis as compared to KL=0 or 1 for the pain were estimated by logistic regression analysis after adjustment for age and BMI, KL=2 spondylosis was not significantly associated with the pain in either gender at any intervertebral level (Table 5). However, KL≥3 spondylosis was related at all levels in women while in none of the levels in men. Further, the number of intervertebral level with KL≥3 spondylosis was significantly associated with low back pain in women ($p<0.01$), but not in men by multiple regression analysis after adjustment for age and BMI. The association between KL≥3 spondylosis at the severest level and low back pain in women was conspicuous in younger

generations (<70 and 70-79) (Supplementary Table 1) and in the urban community (Supplementary Table 2).

DISCUSSION

The present study revealed that the prevalence of radiographic lumbar spondylosis with KL≥2 and KL≥3 in the elderly (≥ 60 years) was 75.8 and 50.4% respectively, and that of low back pain was 28.8% in the overall population. Although the KL≥2 spondylosis was more prevalent in men (84.1%) than in women (70.7%), the KL≥2 spondylosis and low back pain were more prevalent in women. This study also showed that KL=2 spondylosis was not significantly associated with low back pain compared to KL=0 or 1, while KL≥3 spondylosis was related to the pain only in women.

Most previous epidemiologic studies on lumbar spondylosis were focused on the middle-aged or younger populations, reporting the prevalence to be 46.5-83.7% (4,6-8,10,11). Our previous small-scale study on a younger population has shown that to be 76.3 and 37.4% (9). Interestingly, the subjects were living in a mountainous area in Japan, which was shown to have a lower risk for spondylosis in the present study. The variability may therefore be due to the differences of age, community, the sample size and ethnic variation. In fact, a study on the elderly (≥ 65 years) showed that the prevalence of KL≥2 spondylosis was 84.8 and 70.6%, similar to the present results, although in a relatively small number of subjects (5). We have reported different prevalence of lumbar spondylosis in Japan and the United Kingdom by a small-scale comparative study (9), which may in part relate to ethnic variation. It should be noticed that this is the first population-based study that investigated the age-related prevalence of lumbar spondylosis in the elderly. Although KL≥2 and KL≥3 spondylosis tended to increase with age, significant difference was detected between the sixties and the seventies, but not thereafter. However, this cross-sectional analysis, of course, does not lead to the conclusion that individual lumbar spondylosis hardly progresses after 80 years. Since the ROAD study is a prospective cohort study for more than ten years, the follow-up data will clarify the progression with aging. Furthermore, there was a difference of the prevalence between urban and mountainous communities. Considering that lumbar spondylosis is a common disease whose progression is governed by environmental and genetic factors, the regional difference is inevitable, as previously reported (6). Although age and obesity are known to be representative risk factors for lumbar spondylosis (2), the difference between communities in the present study was significant even after adjustment for age and BMI, indicating the involvement of other factors. Here again, further longitudinal survey in the ROAD study that collects database including detailed environmental and genomic information will elucidate the underlying backgrounds.

Interestingly, KL≥2 spondylosis was more prevalent in men than in women, while KL≥3 spondylosis was more prevalent in women. We and others also have reported that osteophytosis of lumbar spine was more common in men than in women (8,9), while disc space narrowing was prevalent in women (9). Based on the definition of the KL grading (12), the discrepancy may be due to distinct etiologic mechanisms between osteophyte formation and disc space narrowing. A cross-sectional study which investigated the extent, prevalence and distribution of spinal spondylosis in women also showed that osteophytosis and disc space narrowing were significantly correlated, but each predicted only 19% of the variation in the other (11). A previous prospective study in knee joints using a famous cohort, the Chingford Study, has