with disc space narrowing but no osteophytosis is unclear. In addition, in terms of the lumbar spine, we did not include lumbar spinal canal stenosis (LSCS), scoliosis, spondylolisthesis, or narrowing of the nerve canal in our analysis, although these changes are also associated with QOL. To determine the associations of these changes of the lumbar spine and knee with QOL, we are currently developing a computer-aided diagnostic program to enable automatic measurement of the major features of VFx, disc space narrowing, osteophytosis, LSCS, scoliosis, spondylosis, and narrowing of the nerve canal in the lumbar spine, and of joint space narrowing and osteophytosis at the knee on plain radiographs [43]. Third, we did not include the onset of VFx in the analysis, although the severity of low back pain often appears to be associated with the interval from the onset of VFx. With respect to clinical fractures, we examined the history of fracture, including vertebral fracture, in the ROAD study by self-report, and no clinical vertebral fractures occurred within 1 month prior to baseline examination. However, we could not compare radiographs of the lumbar spine at baseline examination with those before the examination as the subjects had not undergone radiography of the lumbar spine prior to that examination. We were therefore unable to assess the incidence of subclinical fracture within the month prior to the baseline examination. Both clinical and subclinical vertebral fractures are associated with lower QOL in women [44], but the association between the severity of low back pain and the interval from onset of subclinical VFx may be weaker than that for clinical VFx; consequently, the absence of data on the incidence of subclinical VFx may not strongly affect the present results.

In conclusion, the results of our cross-sectional study using a large-scale population (1,369 Japanese women $\geq$40 years of age) from the ROAD study reveal that knee pain and low back pain were significantly associated with the QOL of these women. In women with knee pain, KL = 4 knee OA was strongly associated with QOL loss. In women with low back pain, no significant associations were seen between KL grade and QOL, while VFx may have some associations with QOL loss. The impact of knee pain with KL = 4 knee OA for PCS was larger than that of low back pain with VFx. Future studies, along with the continued longitudinal survey in the ROAD study, will elucidate the environmental and genetic backgrounds of knee pain and low back pain.

Acknowledgments This study was supported by a Grant-in-Aid for Scientific Research (B20390182, C20591737, C20591774) for Young Scientists (A18689031) and for Exploratory Research (19659305) from the Japanese Ministry of Education, Culture, Sports, Science and Technology, H17-Men-eki-009, H18-Choujyu-037, and H20-Choujyu-009 from the Ministry of Health, Labor and Welfare, Research Aid from the Japanese Orthopaedic Association, and Grant No. 166 from the Japan Orthopaedics and Traumatology Foundation. The authors wish to thank Dr. Anamizu and members of the Department of Orthopaedics, Mr. Kutsuma and other members of the Department of Radiology at Tokyo Metropolitan Geriatric Medical Center, Ms. Tomoko Takijiri and other members of the Public Office in Hidakagawa Town, and Ms. Tamako Tsutsumi, Ms. Kanami Maeda, and other members of the Public Office in Taiji Town for their assistance in locating and scheduling participants for examinations.

Conflict of interest statement None.

References

1. Muraki S, Oka H, Mabuchi A, Akune T, En-yo Y, Yoshida M, et al. Prevalence of radiographic lumbar spondylosis and its association with low back pain in the elderly of population-based cohorts: the ROAD study. Ann Rheum Dis. 2009;68:1401–6.
2. Dawson J, Linsell L, Zondervan K, Rose P, Carr A, Randall T, et al. Impact of persistent hip or knee pain on overall health status in elderly people: a longitudinal population study. Arthritis Rheum. 2005;53:368–74.
3. Muraki S, Oka H, Akune T, Mabuchi A, En-yo Y, Yoshida M, et al. Prevalence of radiographic knee osteoarthritis and its association with knee pain in the elderly of Japanese population-based cohorts: the ROAD study. Osteoarthritis Cartil. 2009;17:1137–43.
4. Hopman-Rock M, Kraaimaat FW, Bijlsma JW. Quality of life in elderly subjects with pain in the hip or knee. Qual Life Res. 1997;6:67–76.
5. Horng YS, Hwang YH, Wu HC, Liang HW, Mhe YJ, Twu FC, et al. Predicting health-related quality of life in patients with low back pain. Spine. 2005;30(5):551–5.
6. Kovacs FM, Abraira V, Zamora J, Teresa Gil del Real M, Llobera J, Fernandez C, et al. Correlation between pain, disability, and quality of life in patients with common low back pain. Spine. 2004;29(2):206–10.
7. Leidig-Bruckner G, Minne HW, Schlaich C, Wagner G, Scheidt-Nave C, Bruckner T, et al. Clinical grading of spinal osteoporosis: quality of life components and spinal deformity in women with chronic low back pain and women with vertebral osteoporosis. J Bone Miner Res. 1997;12(4):663–75.
8. Silverman SL, Piziak VK, Chen P, Misurski DA, Wagman RB. Relationship of health related quality of life to prevalent and new or worsening back pain in postmenopausal women with osteoporosis. J Rheumatol. 2005;32(12):2405–9.
9. Hardt J, Jacobsen C, Goldberg J, Nickel R, Buchwald D. Prevalence of chronic pain in a representative sample in the United States. Pain Med. 2008;9(7):803–12.
10. Bagge E, Bjelle A, Eden S, Svanborg A. Osteoarthritis in the elderly: clinical and radiographic findings in 79 and 85 year olds. Ann Rheum Dis. 1991;50:535–9.
11. Dekker J, Boot B, van der Woude LHV, Bijlsma JWJ. Pain and disability in osteoarthritis: a review of biobehavioral mechanisms. J Behav Med. 1992;15:189–214.
12. Ross PD. Clinical consequences of vertebral fractures. Am J Med. 1997;103:30S–42S.
13. Yoshimura N, Muraki S, Oka H, Mabuch A, En-yo Y, Yoshida M, et al. Prevalence of knee osteoarthritis, lumbar spondylosis and osteoporosis in Japanese men and women: the research on osteoarthritis/osteoporosis against disability (ROAD). J Bone Miner Metab. 2009;27:620–8.
14. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K. Cohort profile: Research on Osteoarthritis/Osteoporosis Against

Disability (ROAD) study. Int J Epidemiol. 2010. doi:10.1093/ije/dyp276.
15. Fukuhara S, Suzukamo Y. Manual of the SF-8 Japanese version (in Japanese). Kyoto: Institute for Health Outcome and Process Evaluation Research; 2004.
16. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35:1095–108.
17. Barr S, Bellamy N, Buchanan WW, Chalmers A, Ford PM, Kean WF, et al. A comparative study of signal versus aggregate methods of outcome measurement based on the WOMAC osteoarthritis index. J Rheumatol. 1994;21:2106–12.
18. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15:1833–40.
19. Inoue T. Clinical features and findings: osteoporosis (in Japanese). Bone. 1990;4:39–47.
20. Kellgren JH, Lawrence JS, editors. The epidemiology of chronic rheumatism: atlas of standard radiographs of arthritis. Oxford: Blackwell; 1963.
21. Ware JE, Snow KK, Kolinski M, Gandeck B. SF-36 health survey manual and interpretation guide. Boston: The Health Institute, New England Medical Centre; 1993.
22. Japanese EuroQol Translation Team. The development of the Japanese EuroQol instrument. J Health Care Soc (in Japanese). 1997;8:23–109.
23. Hashimoto H, Hanyu T, Sledge CB, Lingard EA. Validation of a Japanese patient-derived outcome scale for assessing total knee arthroplasty: comparison with Western Ontario and McMaster Universities osteoarthritis index (WOMAC). J Orthop Sci. 2003;8:288–93.
24. Saito T, Koshino T. Distribution of neuropeptides in synovium of the knee with osteoarthritis. Clin Orthop Relat Res. 2000;376:172–82.
25. 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.
26. Teichtahl AJ, Wluka AE, Morris ME, Davis SR, Cicuttini FM. The relationship between the knee adduction moment and knee pain in middle-aged women without radiographic osteoarthritis. J Rheumatol. 2006;33:1845–8.
27. Thorp LE, Sumner DR, Wimmer MA, Block JA. Relationship between pain and medial knee joint loading in mild radiographic knee osteoarthritis. Arthritis Rheum. 2007;57:1254–60.
28. Felson DT, Niu J, Guermazi A, Roemer F, Aliabadi P, Clancy M, et al. Correlation of the development of knee pain with enlarging bone marrow lesions on magnetic resonance imaging. Arthritis Rheum. 2007;56:2986–92.
29. Symmons DP, van Hemert AM, Vandenbroucke JP, Valkenburg HA. A longitudinal study of back pain and radiological changes in the lumbar spines of middle aged women. II. Radiographic findings. Ann Rheum Dis. 1991;50:162–6.
30. O'Neill TW, McCloskey EV, Kanis JA, Bhalla AK, Reeve J, Reid DM, et al. The distribution, determinants, and clinical correlates of vertebral osteophytosis: a population based survey. J Rheumatol. 1999;26:842–8.
31. Parkkola R, Rytokoski U, Kormano M. Magnetic resonance imaging of the discs and trunk muscles in patients with chronic low back pain and healthy control subjects. Spine. 1993;18:830–6.
32. Boden SD, Davis DO, Dina TS, Patronas NJ, Wiesel SW. Abnormal magnetic-resonance scans of the lumbar spine in asymptomatic subjects. A prospective investigation. J Bone Joint Surg Am. 1990;72:403–8.
33. Sarzi-Puttini P, Atzeni F, Fumagalli M, Capsoni F, Carrabba M. Osteoarthritis of the spine. Semin Arthritis Rheum. 2005;34:38–43.
34. Hicks GE, Simonsick EM, Harris TB, Newman AB, Weiner DK, Nevitt MA, et al. Cross-sectional associations between trunk muscle composition, back pain, and physical function in the health, aging and body composition study. J Gerontol A Biol Sci Med Sci. 2005;60:882–7.
35. Lips P, Cooper C, Agnusdei D, Caulin F, Egger P, Johnell O, et al. Quality of life in patients with vertebral fractures. Validation of the quality of life questionnaire of the European Foundation for Osteoporosis (QUALEFFO). Osteoporos Int. 1999;10:150–60.
36. Silverman SL, Minshall ME, Shen W, Harper KD, Xie S. The relationship of health-related quality of life to prevalent and incident vertebral fractures in postmenopausal women with osteoporosis: results from the multiple outcomes of raloxifene evaluation study. Arthritis Rheum. 2001;44:2611–9.
37. Adachi JD, Ioannidis G, Pickard L, Berger C, Prior JC, Joseph L, et al. The association between osteoporotic fractures and health-related quality of life as measured by the health utilities index in the Canadian multicentre osteoporosis study (CaMos). Osteoporos Int. 2003;14:895–904.
38. Kessler RC, Andrews G, Colpe LJ, Hiripi E, Mroczek DK, Normand SL, et al. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. Psychol Med. 2002;32:959–76.
39. Brage S, Sandanger I, Nygard JF. Emotional distress as a predictor for low back disability: a prospective 12-year population-based study. Spine. 2007;32:269–74.
40. Hill CL, Gill T, Taylor AW, Daly A, Grande ED, Adams RJ. Psychological factors and quality of life in arthritis: a population-based study. Clin Rheumatol. 2007;26:1049–54.
41. Geisser ME, Roth RS. Knowledge of and agreement with chronic pain diagnosis: relation to affective distress, pain beliefs and coping, pain intensity and disability. J Occup Rehabil. 1998;8:73–88.
42. Mason VL, Mathias B, Skevington SM. Accepting low back pain: is it related to a good quality of life? Clin J Pain. 2008;24:22–9.
43. Oka H, Muraki S, Akune T, Mabuchi A, Suzuki T, Yoshida H, et al. Fully automatic quantification of knee osteoarthritis severity on plain radiographs. Osteoarthritis Cartil. 2008;16:1300–6.
44. Adachi JD, Ioannidis G, Pickard L, Berger C, Prior JC, Joseph L, et al. The association between osteoporotic fractures and health-related quality of life as measured by the health utilities index in the Canadian Multicentre Osteoporosis Study (CaMos). Osteoporos Int. 2003;14:895–904.

J Bone Miner Metab (2011) 29:96–102
DOI 10.1007/s00774-010-0197-9

ORIGINAL ARTICLE

Capacity of endogenous sex steroids to predict bone loss in Japanese men: 10-year follow-up of the Taiji Cohort Study

Noriko Yoshimura · Shigeyuki Muraki · Hiroyuki Oka · Hiroshi Kawaguchi · Kozo Nakamura · Toru Akune

Received: 5 January 2010 / Accepted: 2 May 2010 / Published online: 22 June 2010

Abstract This prospective cohort study aimed to evaluate the capacity of endogenous sex steroids to predict male osteoporosis (OP) among community-dwelling inhabitants. Among 1,028 male residents aged 40–79 years, 50 men belonging to each age stratum (200 in total) were randomly selected from a resident registration list. In the years 1993, 1996, 2000, and 2003, bone mineral density (BMD) of the lumbar spine and proximal femur was measured by dual-energy X-ray absorptiometry. Serum total estradiol (E_2) and free testosterone (FT) were measured using samples extracted in 1993. Among the 200 participants at baseline, 153 subjects completed 10-year follow-ups. Mean values of serum E_2 and FT were 22.4 and 9.4 pg/ml, respectively. Rates of change for BMD at the lumbar spine and femoral neck were 0.8% and 0.5% during the first 3 years, 0.0% and 0.5% during 7 years, and 0.8% and –0.3% over 10 years, respectively. According to multivariate regression analysis after adjusting for age and body mass index, mean values of FT were significantly related to the rate of change of BMD at the femoral neck at 3 years (beta = 0.21; $r^2 = 0.05$; $P < 0.01$), but not at 7 or 10 years. Serum FT level could offer a useful predictor of bone loss within 3 years.

Keywords Testosterone · Estrogen · Bone loss · Male osteoporosis · Population-based cohort study

N. Yoshimura (✉) · H. Oka
Department of Joint Disease Research,
22nd Century Medical and Research Center,
Graduate School of Medicine, The University of Tokyo,
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
e-mail: yoshimuran-ort@h.u-tokyo.ac.jp

S. Muraki · T. Akune
Department of Clinical Motor System Medicine,
22nd Century Medical and Research Center,
Graduate School of Medicine,
The University of Tokyo, Tokyo, Japan

H. Kawaguchi · K. Nakamura
Department of Orthopaedic Surgery, Faculty of Medicine,
The University of Tokyo, Tokyo, Japan

Introduction

Osteoporosis (OP) is associated with impairment of activities of daily living (ADL) and quality of life (QOL), leading to increased morbidity and mortality in the elderly [1, 2]. As the proportion of the elderly population is rapidly increasing, an urgent need exists for the development of methods to prevent OP. The estimated number of patients with OP in Japan is about 10 million [3], and cases of hip fracture, as the most severe complication of OP and a key cause of bedridden status, are increasing annually, according to the results of a national survey [4].

Although OP is widely considered as a disorder that mainly affects women, 13% of cases of lumbar spine OP and 24% of cases of femoral neck OP involve men [3]. Up to 20% of hip fractures occur in men, and the number of men with fractures has been rising in Japan [3, 4]. In addition, several studies have shown higher mortality rates after hip fracture in men than in women [5–8], suggesting that male OP warrants urgent attention.

Estrogen is a well-known determinant of low bone mass, bone loss, and osteoporotic fracture in women [9–12]. Reports from the study of osteoporotic fracture suggest that in elderly women, undetectable levels of estradiol, which occur in about one-third of the population, are strongly associated with low bone mineral density (BMD), rapid

bone loss, and increased fracture risk [13–15]. In addition, lower androgen concentrations are reportedly weakly associated with lower BMD and rapid bone loss at some skeletal sites [13].

By contrast, less epidemiological evidence has been gathered regarding the influence of serum sex hormone levels on bone loss, OP, and osteoporotic fracture in men. Some studies of BMD in men have reported positive associations with endogenous androgen levels [16–19], but others have found no significant association [20, 21]. The influence of endogenous sex hormone concentrations on bone loss in men thus remains controversial.

In the present study, to clarify the age distribution of serum levels of endogenous sex steroids and to explore the predictive capacity of these levels for bone loss in men for the early detection of male OP, we measured baseline concentrations of endogenous sex steroids in male subjects randomly selected from a rural population in Japan and conducted follow-up for 10 years.

Materials and methods

Establishment of baseline cohort

This survey was performed in the Japanese town of Taiji. The Taiji cohort has been profiled in detail elsewhere [22–24] and so is summarized here only briefly. Taiji is located in the southern coastal area of Wakayama Prefecture. A list of all inhabitants born in 1913–1952, and therefore aged between 40 and 79 years old in 1993, was compiled based on resident registrations as of the end of 1992. A cohort of 2,261 inhabitants (1,028 men, 1,233 women) was identified, and all members of the cohort completed a self-administered, 125-item questionnaire addressing topics such as dietary habits, smoking habits, alcohol consumption, and physical exercise (whole cohort).

From the whole cohort, 50 men in each of four age groups between 40 and 79 years by decade of birth year (1913–1922, 1923–1932, 1933–1942, and 1943–1952), for a total of 200 participants, were randomly selected. BMD was measured for these 200 participants in 1993. At this time, blood samples of all participants were taken. An interviewer administered a second questionnaire to these 200 participants covering items of past medical history, including questions related to osteoporotic fractures and falls, family history, calcium intake, dietary habits, physical exercise, occupational activities, sun exposure, and, for women, additional questions about reproductive variables (baseline study).

Measurements of endogenous sex steroids

At the baseline study in 1993, blood samples were taken from all participants. After centrifugation of blood samples, sera were immediately placed in dry ice, transferred to a freezer within 24 h, and kept at –80°C until assayed. Serum levels of total estradiol (E_2) and free testosterone (FT) were measured using an immunoradiometric assay (DPC-free estradiol kit and DPC-free testosterone kit, respectively; Mitsubishi Kagaku, Tokyo, Japan). The lowest measurable levels of E_2 and FT were 10 and 0.4 pg/ml, respectively, and percent of coefficient of variation (CV%) for E2 and FT were both less than 15% (unpublished data).

BMD measurements

Baseline BMD was measured in 1993 using dual-energy X-ray absorptiometry (DXA) (QDR 1000; Hologic, Bedford, MA, USA), providing anteroposterior images of lumbar vertebrae L2–L4 and the proximal femur (femoral neck, Ward's triangle, trochanter). These measurements were repeated on the same participants after 3, 7, and 10 years (1996, 2000, and 2003).

To control for the precision of DXA, the equipment was checked at every examination in 1993, 1996, 2000, and 2003 using the same phantom, and BMD of the phantom was regulated to 1.030 ± 0.016 g/cm^2 (1.5%) during all examinations. All BMD measurements were performed by the same medical doctor (N.Y.). Intraobserver variability for DXA scans by this investigator was 0.35% using the phantom, as reported previously [25].

Annual rates of change for BMD during 3-, 7-, and 10-year observations were calculated as follows:

$$\text{Annual rate (\%/year)} = [(\text{BMD follow-up} - \text{BMD baseline})/\text{BMD baseline/follow-up years}] \times 100$$

All examinations were performed with the full consent of the participants. These studies were approved by the ethics committees of both Wakayama Medical University and the University of Tokyo.

Statistical analysis

All statistical analyses were performed using STATA statistical software (STATA, College Station, TX, USA). Differences were tested for significance using analysis of variance for comparisons among multiple groups, and Scheffe's least significant difference (LSD) test for pairs of groups. Significant items were selected, and multiple regression analysis was performed with adjustment of suitable variables.

Results

Eligible participants and baseline characteristics

Background data including physical characteristics for all male participants at baseline are shown in Table 1. Mean weight and height in their fifties, sixties, and seventies, and mean body mass index (BMI) in their seventies were significantly lower than those in their forties ($P < 0.05$).

Among the 200 male participants at baseline, 1 man in his sixties declined to undergo blood and urinary examinations for endogenous hormones. Examinations at baseline were thus performed on 199 men. The second visit, aimed at evaluating changes in BMDs over 3 years, obtained measurements for 181 of the 200 initially recruited participants (90.5%). The following reasons were given for the loss of 19 participants at the 3-year follow-up: 8 men had died, 1 man had moved, 1 man was ill, 4 men declined to participate, and 2 men were away from the area at the time of follow-up. The third visit, aimed at evaluating changes in BMDs over 7 years, evaluated 170 of the 200 initially recruited participants (85%). Loss of 30 participants at the 7-year follow-up was explained as follows: 14 men had died, 3 men had moved, 6 men were ill, 5 men declined to participate, and 2 men were away from the area at the time of follow-up. Among the 200 male participants initially recruited, 153 men participated in the fourth visit held in 2003 (76.5%). Loss of 47 participants at the 10-year follow-up was explained as follows: 33 men had died, 6 men had moved, 4 men were ill, 2 men declined to participate, and 2 men were away from the area at the time of follow-up.

Mean levels of serum concentration of sex steroids at baseline

Age distributions of mean E_2 and FT levels at the initial survey are also shown in Table 1. Because data below the measurable range were excluded from analysis, E_2 and FT data could be obtained for 178 and 198 participants, respectively. Mean serum levels of E_2 and FT were 22.4 and 9.4 pg/ml, respectively. Although no significant age-related trends were seen for E_2, a significant trend toward low values of FT was noted according to age ($P < 0.001$). In addition, mean serum FT was significantly higher for men in their forties than for men in their sixties and seventies ($P < 0.05$).

Predictive capacity of endogenous sex steroids for bone change

Initial mean values and rates of change in L2–L4 BMD over the 3-, 7-, and 10-year periods, classified by age stratum, are shown in Table 2. BMD values at L2–L4 for men had increased slightly by the 10-year follow-up in their fifties and sixties but had decreased a little in the forties and seventies. BMD values at the femoral neck over 10 years had decreased for men in their forties and fifties and had increased considerably in their seventies.

According to multivariate regression analysis using each rate of change for BMD at the lumbar spine over 3, 7, and 10 years as an objective factor and serum levels of E_2 as an explanatory factor after adjusting for age and BMI, beta values for the rate of change for BMD for the first 3, 7, and 10 years were 0.02, 0.04, and –0.02, respectively. Similarly, on multivariate regression analysis using each rate of change for BMD at the femoral neck over 3, 7, and 10 years as an objective factor and serum levels of E_2 as an explanatory factor after adjusting for age and BMI, beta values for the rate of change for BMD for the first 3, 7, and 10 years were –0.07, 0.09, and –0.01, respectively. Total E_2 values could not predict bone change at the lumbar spine or femoral neck at 3, 7, or 10 years.

Again, using the results of multivariate regression analysis to clarify associations between serum FT and

Table 1 Summary characteristics for male participants at baseline classified by age

Birth cohort	Age-group (years)	*n*	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	E2 (pg/mL)		FT (pg/mL)	
			Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
1943–1952	40–49	50	44.2 (2.6)	168.8 (5.2)	69.0 (10.4)	24.2 (3.2)	46	22.1 (7.4)	50	10.9 (2.8)
1933–1942	50–59	50	54.8 (2.7)	165.6 (5.0)[a]	63.5 (9.4)[a]	23.1 (2.9)	43	22.2 (7.0)	50	9.8 (2.6)
1923–1932	60–69	50	64.6 (2.5)	163.0 (4.8)[a]	62.9 (9.6)[a]	23.6 (3.2)	46	23.1 (8.5)	49	8.8 (2.6)[a]
1913–1922	70–79	50	74.0 (2.7)	160.7 (5.4)[a,b]	57.5 (8.3)[a,b,c]	22.2 (2.8)[a]	43	22.3 (7.7)	49	8.2 (3.1)[a]
1913–1952	40–79	200	59.4 (11.4)	164.5 (5.9)	63.2 (10.2)	23.3 (3.1)	178	22.4 (7.6)	198	9.4 (2.9)

BMI body mass index, *E2* total estradiol, *FT* free testosterone, *n* number of participants, *SD* standard deviation

[a] Significantly different ($P < 0.05$) from values of participants in their forties

[b] Significantly different ($P < 0.05$) from values of participants in their fifties

[c] Significantly different ($P < 0.05$) from values of participants in their sixties

Table 2 Mean values (SD) of bone mineral density (g/cm^2) and change rate (%) at lumbar spine L2–L4 and femoral neck over 3, 7, and 10 years, classified by age and gender

Birth cohort	Age-group (years)	L2–L4								Femoral neck				
		Baseline		2nd visit (3-year follow-up)		3rd visit (7-year follow-up)		4th visit (10-year follow-up)		Baseline	2nd visit	3rd visit	4th visit	
		n	BMD (g/cm^2)	*n*	Change rate (%/3 years)	*n*	Change rate (%/7 years)	*n*	Change rate (%/10 years)	BMD (g/cm^2)	Change rate (%/3 years)	Change rate (%/7 years)	Change rate (%/10 years)	
1943–1952	40–49	50	1.05 (0.15)	48	0.6 (3.8)	46	−0.6 (5.1)	43	−0.2 (5.8)	0.86 (0.09)	0.3 (4.6)	−1.8 (4.8)	−1.5 (10.9)	
1933–1942	50–59	50	0.98 (0.17)	47	1.0 (3.3)	46	−0.0 (6.3)	46	1.6 (8.0)	0.80 (0.13)[a]	−0.2 (4.9)	0.7 (10.0)	−3.0 (6.8)	
1923–1932	60–69	50	1.04 (0.21)	49	1.3 (3.6)	47	1.4 (7.1)	41	2.3 (9.4)	0.77 (0.11)[a]	1.0 (7.0)	−0.1 (9.3)	0.3 (12.5)	
1913–1922	70–79	50	0.97 (0.19)	37	0.1 (5.3)	31	−1.2 (7.9)	23	−1.5 (9.2)	0.71 (0.08)[a,b,c]	0.9 (6.3)	4.6 (10.2)[a]	6.6 (16.2)[b]	
1913–1952	40–79	200	1.01 (0.18)	181	0.8 (4.0)	170	0.0 (6.6)	153	0.8 (8.1)	0.79 (0.12)	0.5 (5.7)	0.5 (8.9)	−0.3 (11.7)	

SD standard deviation, *BMD* bone mineral density, *n* number of participants

[a] Significantly different ($P < 0.05$) from values of subjects in their forties

[b] Significantly different ($P < 0.05$) from values of subjects in their fifties

[c] Significantly different ($P < 0.05$) from values of subjects in their sixties

BMD changes at the lumbar spine and femoral neck, beta values of FT for the rate of change for BMD at the lumbar spine at the first 3, 7, and 10 years were 0.08, 0.08, and 0.03, respectively, and those at the femoral neck were 0.21, 0.14, and 0.06, respectively. Mean FT levels were significantly related to the rate of change for BMD at the femoral neck during the first 3 years ($R^2 = 0.05$, $P < 0.01$), but could not predict bone change at any site at 7 or 10 years.

Discussion

The present study examined endogenous hormone levels among men in Japan, measuring changes in BMD over spans of 3, 7, and 10 years. The present study clarified the age distribution of endogenous sex steroids, and a significant trend was seen toward low FT levels with age. FT tended to be significantly lower in the sixties and older when compared with levels in the forties in the present study. Our results support the findings of other reports. Orwoll et al. [26] showed that testosterone levels, particularly FT levels, for 2,623 men 65 years or older were associated with increasing age. Similar findings have been described in other cross-sectional and longitudinal studies [27–29]. Based on these results, we concluded that older men tended to show lower testosterone levels than younger men, similar to the situation with E_2 in women. Some men might display testosterone insufficiency, as seen in women with E_2 insufficiency. However, we do not yet have enough evidence regarding normal ranges in young men and thresholds for testosterone insufficiency. In addition, levels of testosterone may vary among individuals and be influenced by body composition such as adipose tissue, muscle, and bone.

In contrast to testosterone, no significant age-related trend in E_2 was found in the present study. Little information is available regarding E_2 levels in older men. Orwoll et al. [26] reported that E_2 concentrations decreased as age increased, and similar findings have been described in various reports [30–33]. However, other studies have noted stable [34–36] or rising [37] E_2 levels with increasing age. Although the reasons for these discrepancies are unclear, E_2 levels may vary among individuals and may be influenced by body composition such as adipose tissue, muscle, and bone, as well as testosterone.

Regarding the ethnic variations in serum sex steroid levels, as most previous reports have been based on studies of Caucasian men, ethnic variations in FT levels among men remain unclear. To the best of our knowledge, the Osteoporotic Fractures in Men Study (MrOS) is the only study in which a sufficient number of Asian men have participated [26]. For reasons of differences in measurement methods, direct comparison of the present results and

those from the MrOS study is inappropriate, but FT levels among Japanese men tended to be lower than those in MrOS participants, although no significant difference in E_2 levels was apparent. Orwoll et al. [26] analyzed ethnic differences in the MrOS study and stated that FT levels were lower in Asian men than in other races such as Caucasian, African-American, and Hispanic subjects, but no such differences were seen for E_2. The present results support these findings.

The present study found that serum levels of FT could offer a useful predictor of bone loss at the femoral neck within 3 years, but this effect was diluted with longer observation. Regarding the effects of testosterone on bone loss at the hip, Cauley et al. [38] reported, in an epidemiological study of 1,327 men ≥65 years old, that men in the lowest FT category experienced greater hip bone loss over 1.8 years. In addition, Ensrud et al. [39] reported that among men with weight loss, the rate of decline in total hip BMD showed a stepwise increase in magnitude with greater decreases in bioavailable testosterone from baseline. In the present study, the effect of FT levels on bone loss within the relatively short term up to 3 years was observed at the femoral neck, independent of age and BMI, supporting previous reports. Although reasons for site-specific differences in the predictive capacity of FT remain uncertain, we have already reported that bone loss rate differs depending on the site involved in another cohort study [40]. We have also reported that characteristics differ between fast bone losers at the lumbar spine and femoral neck [41]. One reason for site-specific differences might be because degenerative changes that increase BMD, such as osteophytosis or sclerotic change, are observed more frequently at the lumbar spine than at the femoral neck. These results suggest that the predictive capacity of FT might differ according to the sites involved.

A recent study showed that older men with total testosterone or E_2 deficiency were more likely to be osteoporotic [19], but no report evaluated the capacity of serum sex steroids to predict occurrence of OP. Regarding the relationship between testosterone and fracture risk, Mellstrom et al. [42] reported that FT within the normal range was independently associated with the presence, but not occurrence, of osteoporotic fracture in elderly men. In contrast, an analysis from the Rotterdam Study failed to confirm any association between testosterone and fracture risk [43]. Data from the Framingham study indicated that men with low serum testosterone and E_2 levels were at increased risk for incident hip fractures [44]. A recent report from the Dubbo osteoporosis epidemiology study revealed that in men older than 60 years, serum testosterone is independently associated with the risk of osteoporotic fracture [45]. We also tried to evaluate the predictive capacity of serum levels of sex steroids and occurrence of OP based on WHO criteria [46] and osteoporotic fractures, but only identified 7 cases of OP and 10 cases of osteoporotic fractures including 1 vertebral fracture, 1 hip fracture, 2 wrist fractures, 3 costal fractures, 2 ankle fractures, and 1 finger fracture. After analysis using Cox proportional hazards models adjusted for age and BMI, serum levels of FT were significantly related to incidence of OP (hazard ratio, 0.42; 95% confidence interval, 0.19–0.90), but not to incidence of osteoporotic fractures. This analysis suggests the possibility of serum FT as a predictor for OP occurrence over 10 years. However, the number of occurrences of OP seems to be too small to reach any conclusion regarding the presence or absence of associations between sex steroids and OP or osteoporotic fractures.

There are several limitations in the present study. First, the small sample size seemed to be the most severe weakness. In fact, as already noted, only 7 cases of OP and 10 cases of osteoporotic fractures were accumulated during the 10 years of the study. Longer observation in the present cohort might be required to confirm the association between sex steroids and OP or osteoporotic fracture. Second, the dropout rate over 10 years for patients in their seventies was considerably high (54.0%). This high dropout rate might cause bias. In fact, the tendency toward an increase in BMD at the femoral neck for patients in their seventies was skewed by withdrawal bias. On the basis of this hypothesis, we reanalyzed the multivariate regression analysis to assess the change rate of BMD at the femoral neck and serum FT with exclusion of subjects in their seventies. However, the results were similar, with serum levels of FT predicting bone loss at the femoral neck within 3 years (beta = 0.17, $P = 0.05$), but diluted effects with longer observation (7 years: beta = 0.8, $P = 0.38$; 10 years: beta = 0.03, $P = 0.77$). Third, all serum samples were extracted between 0900 and 1500, not at a fixed time in the morning, although samples for measurement of FT are recommended to be collected in the morning. Serum levels of testosterone tend to increase toward night, peaking in the early morning, then decreasing rapidly and reaching a nadir between 1300 and 2300. We collected samples when FT levels would probably have been decreasing toward the nadir. The present study might thus have underestimated FT values compared to collection at a fixed time in the morning.

Conversely, the study design shows several notable strengths. In this population-based cohort study, subjects were selected randomly from the resident registration list. BMD was carefully measured by a single observer (N.Y.), and measurements were repeated 3, 7, and 10 years later with high participation rate by the same device and same observer. Another strength was that the effect of serum levels of sex steroids on changes in BMD could be estimated directly.

In conclusion, we clarified that serum levels of FT could predict bone loss within 3 years, but not longer. Further observations are required to confirm the relationship between FT, E_2, and spinal OP and osteoporotic fractures. Other environmental and genetic factors should also be evaluated to develop strategies for the early prevention of OP.

Acknowledgments This work was supported by Grants-in-Aid for Scientific Research: B20390182 (Noriko Yoshimura), C20591737 (Toru Akune), C20591774 (Shigeyuki Muraki), and Young Scientists A18689031 (Hiroyuki Oka) and Collaborating Research with NSF 08033011-00262 (Director, Noriko Yoshimura) from the Ministry of Education, Culture, Sports, Science and Technology, H17-Men-eki-009 (Director, Kozo Nakamura), H18-Choujyu-037 (Director, Toshitaka Nakamura) and H20-Choujyu-009 (Director, Noriko Yoshimura) from the Ministry of Health, Labour and Welfare in Japan. This study was also supported by grants from the Japan Osteoporosis Society (Noriko Yoshimura), Nakatomi Foundation (Noriko Yoshimura) and research aid from the Japanese Orthopaedic Association (JOA-Subsidized Science Project Research 2006-1, Director, Hiroshi Kawaguchi). The sponsors played no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The authors thank Mrs. Tamako Tsutsumi, Mrs. Kanami Maeda, and other members in the Public Office in Taiji Town and members of the Public Health Center in Shingu City for their assistance in the location and scheduling of participants for examinations.

Conflict of interest statement The authors have no conflicts/disclosures to declare regarding the present manuscript.

References

1. Jornell O, Kanis JA, Oden A, Sembo I, Redlund-Johnell I, Petterson C, De Laet C, Jonsson B (2004) Mortality after osteoporotic fractures. Osteoporosis Int 15:38–42
2. Muraki S, Yamamoto S, Ishibashi H, Nakamura K (2006) Factors associated with mortality following hip fracture in Japan. J Bone Miner Metab 24:100–104
3. Yoshimura N, Muraki S, Oka H, Mabuchi A, En-yo Y, Yoshida M, Saika A, Suzuki T, Yoshida H, Kawaguchi H, Nakamura K, Akune T (2009) Prevalence of knee osteoarthritis, lumbar spondylosis and osteoporosis in Japanese men and women: the research on osteoarthritis/osteoporosis against disability study. J Bone Miner Metab 27:620–628
4. Sakata T, Yaegashi Y, Hosoi T, Orimo H (2009) The 2007 nationwide survey on the incidence of hip fracture in Japan and 20-year trends. Osteoporos Int 20(suppl 1):S63
5. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA (1999) Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet 353:878–882
6. Seeman E (2004) Osteoporosis in men. In: Seeman E (ed) Invest in your bones. International Osteoporosis Foundation, Nyon, Switzerland, pp 1–16
7. Amin S, Felson DT (2001) Osteoporosis in men. Rheum Dis Clin N Am 27:19–47
8. Forsen L, Sogaard AJ, Meyer HE, Edna T, Kopjar B (1999) Survival after hip fracture, short- and long-term excess mortality according to age and gender. Osteoporos Int 10:73–78
9. Riis BJ, Rodbro P, Christiansen D (1986) The role of serum concentrations of sex steroids and bone turnover in the development and occurrence of postmenopausal osteoporosis. Calcif Tissue Int 38:318–322
10. Slemenda C, Hui SL, Longscope C, Johnston CC (1987) Sex steroids and bone mass: a study of changes about the time of menopause. J Clin Invest 80:1261–1269
11. Slemenda C, Longscope C, Peacock M, Hui S, Johnston CC (1996) Sex steroids, bone mass and bone loss. J Clin Invest 97:14–21
12. Yoshimura N, Kasamatsu T, Sakata K, Hashimoto T, Cooper C (2002) The relationship between endogenous estrogen, sex hormone binding globulin and bone loss in female residents of a rural Japanese community: the Taiji study. J Bone Miner Metab 20:303–310
13. Ettinger B, Pressman A, Sklarin P, Bauer D, Cauley JA, Cummings SR (1998) Associations between low levels of serum estradiol, bone density, and fractures among elderly women: the study of osteoporotic fractures. J Clin Endocrinol Metab 83:2239–2243
14. Stone K, Bauer DC, Black DM, Sklarin P, Ensrud KE, Cummings SR (1998) Hormonal predictors of bone loss in elderly women: a prospective study. J Bone Miner Res 13:1167–1174
15. Cummings SR, Browner WS, Bauer DB, Stone K, Ensrud K, Jamal S, Ettinger B (1998) Endogenous hormones and the risk of hip and vertebral fractures among older women. N Engl J Med 339:733–738
16. Murphy S, Khaw KT, Cassidy A, Compston JE (1993) Sex hormones and bone mineral density in elderly men. Bone Miner 20:133–140
17. Ongphiphadhanakul B, Rajatanavin R, Chailurkit L, Piaseu N, Teerarungsikul K, Sirisriro R, Komindr S, Puavilai G (1995) Serum testosterone and its relation to bone mineral density and body composition in normal males. Clin Endocrinol (Oxf) 43:727–733
18. Rucker D, Ezzat S, Diamandi A, Khosravi J, Hanley DA (2004) IGF-I and testosterone levels as predictors of bone mineral density in healthy, community-dwelling men. Clin Endocrinol (Oxf) 60:491–499
19. Fink HA, Ewing SK, Ensrud KE, Barrett-Connor E, Taylor BC, Cauley JA, Orwoll ES (2006) Association of testosterone and estradiol deficiency with osteoporosis and rapid bone loss in older men. J Clin Endocrinol Metab 91:3908–3915
20. Van Pottelbergh I, Goemaere S, Kaufman JM (2003) Bioavailable estradiol and an aromatase gene polymorphism are determinants of bone mineral density changes in men over 70 years of age. J Clin Endocrinol Metab 88:3075–3081
21. Gennari L, Merlotti D, Martini G, Gonnelli S, Franci B, Campagna S, Lucani B, Dal Canto N, Valenti R, Gennari C, Nuti R (2003) Longitudinal association between sex hormone levels, bone loss, and bone turnover in elderly men. J Clin Endocrinol 88:5327–5333
22. Kasamatsu T, Yoshimura N, Morioka S, Sugita K, Hashimoto T (1996) A population survey on bone mineral density in a fishing village in Wakayama Prefecture (Part 1). Distribution of bone mineral density by sex and age on a representative sample of the community. Jpn J Hyg 50:1084–1092 (in Japanese)
23. Yoshimura N, Kasamatsu T, Morioka S, Hashimoto T (1996) A population survey on bone mineral density in a fishing village in Wakayama Prefecture (Part 2). The analysis of the risk factors affecting the bone mineral density. Jpn J Hyg 51:677–684 (in Japanese)
24. 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
25. 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 (DPX-L). J Wakayama Med Soc 48:461–466
26. Orwoll E, Lambert LC, Marshall LM, Phipps K, Blank J, Barrett-Connor E, Cauley J, Ensrud K, Cummings S (2006) Testosterone and estradiol among older men. J Clin Endocrinol Metab 91:1336–1344
27. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR, Baltimore Longitudinal Study of Aging (2001) Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 86:724–731
28. Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB (2002) Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab 87:589–598
29. Liu PY, Beilin J, Meier C, Nguyen TV, Center JR, Leedman PJ, Seibel MJ, Eisman JA, Handelsman DJ (2007) Age-related changes in serum testosterone and sex hormone binding globulin in Australian men: longitudinal analyses of two geographically separate regional cohorts. J Clin Endocrinol Metab 92:3599–3603
30. Khosla S, Melton LJ, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL (1998) Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. J Clin Endocrinol Metab 83:2266–2274
31. Khosla S, Melton J III, Atkinson EJ, O'Fallon WM (2001) Relationship of serum sex steroid levels to longitudinal changes in bone density in young versus elderly men. J Clin Endocrinol Metab 86:3555–3561
32. van den Beld AW, de Jong FH, Grobbee DE, Pols HA, Lamberts SW (2000) Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density, and body composition in elderly men. J Clin Endocrinol Metab 85:3276–3282
33. Leifke E, Gorenoi V, Wichers C, Von Zur Muhlen A, Von Buren E, Brabant G (2000) Age-related changes of serum sex hormones, insulin-like growth factor-1 and sex-hormone binding globulin levels in men: cross-sectional data from a healthy male cohort. Clin Endocrinol (Oxf) 53:689–695
34. Gray A, Feldman HA, McKinlay JB, Longcope C (1991) Age, disease and changing sex hormone levels in middle-aged men: results of the Massachusetts male aging study. J Clin Endocrinol Metab 73:1016–1025
35. Muller M, den Tonkelaar I, Thijssen JH, Grobbee DE, van der Schouw YT (2003) Endogenous sex hormones in men aged 40–80 years. Eur J Endocrinol 149:583–589
36. Belanger A, Candas B, Dupont A, Cusan L, Diamond P, Gomez JL, Labrie F (1994) Changes in serum concentrations of conjugated and unconjugated steroids in 40- to 80-year-old men. J Clin Endocrinol Metab 79:1086–1090
37. Bjornerem A, Straume B, Midtby M, Fonnebo V, Sundsfjord J, Svartberg J, Acharya G, Oian P, Berntsen GK (2004) Endogenous sex hormones in relation to age, sex, lifestyle factors, and chronic diseases in a general population: the Tromso Study. J Clin Endocrinol Metab 89:6039–6047
38. Cauley J, Taylor B, Fink H, Ensrud K, Bauer D, Barrett-Connor E, Marshall L, Nevitt M, Stefanick M, Orwoll E (2004) Sex steroid hormones in older men: cross-sectional and longitudinal associations with bone mineral density (BMD). The Osteoporotic Fracture in Men Study (MrOS). J Bone Miner Res 19(suppl 1):S16
39. Ensrud KE, Lewis CE, Lambert LC, Taylor BC, Fink HA, Barrett-Connor E, Cauley JA, Stefanick ML, Orwoll E, Osteoporotic Fractures in Men MrOS Study Research Group (2006) Endogenous sex steroids weight change and rates of hip bone loss in older men: the MrOS study. Osteoporos Int 17:1329–1336
40. 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
41. Yoshimura N, Takijiri T, Kinoshita H, Danjoh S, Kasamatsu T, Morioka S, Sakata K, Hashimoto T, Takeshita T (2004) Characteristics and course of bone mineral densities among fast bone losers in a rural Japanese community: the Miyama study. Osteoporos Int 15:139–144
42. Mellström D, Johnell O, Ljunggren O, Eriksson AL, Lorentzon M, Mallmin H, Holmberg A, Redlund-Johnell I, Orwoll E, Ohlsson C (2006) Free testosterone is an independent predictor of BMD and prevalent fractures in elderly men: MrOS Sweden. J Bone Miner Res 21:529–535
43. Goderie-Plomp HW, van der Klift M, de Ronde W, Hofman A, de Jong FH, Pols HA (2004) Endogenous sex hormones, sex hormone-binding globulin, and the risk of incident vertebral fractures in elderly men and women: the Rotterdam Study. J Clin Endocrinol Metab 89:3261–3269
44. Amin S, Zhang Y, Felson DT, Sawin CT, Hannan MT, Wilson PW, Kiel DP (2006) Estradiol, testosterone, and the risk for hip fractures in elderly men from the Framingham Study. Am J Med 119:426–433
45. Meier C, Nguyen TV, Handelsman DJ, Schindler C, Kushnir MM, Rockwood AL, Meikle AW, Center JR, Eisman JA, Seibel MJ (2008) Endogenous sex hormones and incident fracture risk in older men: the Dubbo Osteoporosis Epidemiology Study. Arch Intern Med 168:47–54
46. World Health Organization (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. WHO Technical Report Series 843. WHO, Geneva

J Bone Miner Metab (2011) 29:96–102
DOI 10.1007/s00774-010-0197-9

ORIGINAL ARTICLE

Capacity of endogenous sex steroids to predict bone loss in Japanese men: 10-year follow-up of the Taiji Cohort Study

Noriko Yoshimura · Shigeyuki Muraki · Hiroyuki Oka · Hiroshi Kawaguchi · Kozo Nakamura · Toru Akune

Received: 5 January 2010 / Accepted: 2 May 2010 / Published online: 22 June 2010

Abstract This prospective cohort study aimed to evaluate the capacity of endogenous sex steroids to predict male osteoporosis (OP) among community-dwelling inhabitants. Among 1,028 male residents aged 40–79 years, 50 men belonging to each age stratum (200 in total) were randomly selected from a resident registration list. In the years 1993, 1996, 2000, and 2003, bone mineral density (BMD) of the lumbar spine and proximal femur was measured by dual-energy X-ray absorptiometry. Serum total estradiol (E_2) and free testosterone (FT) were measured using samples extracted in 1993. Among the 200 participants at baseline, 153 subjects completed 10-year follow-ups. Mean values of serum E_2 and FT were 22.4 and 9.4 pg/ml, respectively. Rates of change for BMD at the lumbar spine and femoral neck were 0.8% and 0.5% during the first 3 years, 0.0% and 0.5% during 7 years, and 0.8% and –0.3% over 10 years, respectively. According to multivariate regression analysis after adjusting for age and body mass index, mean values of FT were significantly related to the rate of change of BMD at the femoral neck at 3 years (beta = 0.21; $r^2 = 0.05$; $P < 0.01$), but not at 7 or 10 years. Serum FT level could offer a useful predictor of bone loss within 3 years.

Keywords Testosterone · Estrogen · Bone loss · Male osteoporosis · Population-based cohort study

N. Yoshimura (✉) · H. Oka
Department of Joint Disease Research,
22nd Century Medical and Research Center,
Graduate School of Medicine, The University of Tokyo,
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
e-mail: yoshimuran-ort@h.u-tokyo.ac.jp

S. Muraki · T. Akune
Department of Clinical Motor System Medicine,
22nd Century Medical and Research Center,
Graduate School of Medicine,
The University of Tokyo, Tokyo, Japan

H. Kawaguchi · K. Nakamura
Department of Orthopaedic Surgery, Faculty of Medicine,
The University of Tokyo, Tokyo, Japan

Introduction

Osteoporosis (OP) is associated with impairment of activities of daily living (ADL) and quality of life (QOL), leading to increased morbidity and mortality in the elderly [1, 2]. As the proportion of the elderly population is rapidly increasing, an urgent need exists for the development of methods to prevent OP. The estimated number of patients with OP in Japan is about 10 million [3], and cases of hip fracture, as the most severe complication of OP and a key cause of bedridden status, are increasing annually, according to the results of a national survey [4].

Although OP is widely considered as a disorder that mainly affects women, 13% of cases of lumbar spine OP and 24% of cases of femoral neck OP involve men [3]. Up to 20% of hip fractures occur in men, and the number of men with fractures has been rising in Japan [3, 4]. In addition, several studies have shown higher mortality rates after hip fracture in men than in women [5–8], suggesting that male OP warrants urgent attention.

Estrogen is a well-known determinant of low bone mass, bone loss, and osteoporotic fracture in women [9–12]. Reports from the study of osteoporotic fracture suggest that in elderly women, undetectable levels of estradiol, which occur in about one-third of the population, are strongly associated with low bone mineral density (BMD), rapid

bone loss, and increased fracture risk [13–15]. In addition, lower androgen concentrations are reportedly weakly associated with lower BMD and rapid bone loss at some skeletal sites [13].

By contrast, less epidemiological evidence has been gathered regarding the influence of serum sex hormone levels on bone loss, OP, and osteoporotic fracture in men. Some studies of BMD in men have reported positive associations with endogenous androgen levels [16–19], but others have found no significant association [20, 21]. The influence of endogenous sex hormone concentrations on bone loss in men thus remains controversial.

In the present study, to clarify the age distribution of serum levels of endogenous sex steroids and to explore the predictive capacity of these levels for bone loss in men for the early detection of male OP, we measured baseline concentrations of endogenous sex steroids in male subjects randomly selected from a rural population in Japan and conducted follow-up for 10 years.

Materials and methods

Establishment of baseline cohort

This survey was performed in the Japanese town of Taiji. The Taiji cohort has been profiled in detail elsewhere [22–24] and so is summarized here only briefly. Taiji is located in the southern coastal area of Wakayama Prefecture. A list of all inhabitants born in 1913–1952, and therefore aged between 40 and 79 years old in 1993, was compiled based on resident registrations as of the end of 1992. A cohort of 2,261 inhabitants (1,028 men, 1,233 women) was identified, and all members of the cohort completed a self-administered, 125-item questionnaire addressing topics such as dietary habits, smoking habits, alcohol consumption, and physical exercise (whole cohort).

From the whole cohort, 50 men in each of four age groups between 40 and 79 years by decade of birth year (1913–1922, 1923–1932, 1933–1942, and 1943–1952), for a total of 200 participants, were randomly selected. BMD was measured for these 200 participants in 1993. At this time, blood samples of all participants were taken. An interviewer administered a second questionnaire to these 200 participants covering items of past medical history, including questions related to osteoporotic fractures and falls, family history, calcium intake, dietary habits, physical exercise, occupational activities, sun exposure, and, for women, additional questions about reproductive variables (baseline study).

Measurements of endogenous sex steroids

At the baseline study in 1993, blood samples were taken from all participants. After centrifugation of blood samples, sera were immediately placed in dry ice, transferred to a freezer within 24 h, and kept at –80°C until assayed. Serum levels of total estradiol (E_2) and free testosterone (FT) were measured using an immunoradiometric assay (DPC-free estradiol kit and DPC-free testosterone kit, respectively; Mitsubishi Kagaku, Tokyo, Japan). The lowest measurable levels of E_2 and FT were 10 and 0.4 pg/ml, respectively, and percent of coefficient of variation (CV%) for E2 and FT were both less than 15% (unpublished data).

BMD measurements

Baseline BMD was measured in 1993 using dual-energy X-ray absorptiometry (DXA) (QDR 1000; Hologic, Bedford, MA, USA), providing anteroposterior images of lumbar vertebrae L2–L4 and the proximal femur (femoral neck, Ward's triangle, trochanter). These measurements were repeated on the same participants after 3, 7, and 10 years (1996, 2000, and 2003).

To control for the precision of DXA, the equipment was checked at every examination in 1993, 1996, 2000, and 2003 using the same phantom, and BMD of the phantom was regulated to 1.030 ± 0.016 g/cm^2 (1.5%) during all examinations. All BMD measurements were performed by the same medical doctor (N.Y.). Intraobserver variability for DXA scans by this investigator was 0.35% using the phantom, as reported previously [25].

Annual rates of change for BMD during 3-, 7-, and 10-year observations were calculated as follows:

$$\text{Annual rate (\%/year)} = [(\text{BMD follow-up} - \text{BMD baseline})/\text{BMD baseline/follow-up years}] \times 100$$

All examinations were performed with the full consent of the participants. These studies were approved by the ethics committees of both Wakayama Medical University and the University of Tokyo.

Statistical analysis

All statistical analyses were performed using STATA statistical software (STATA, College Station, TX, USA). Differences were tested for significance using analysis of variance for comparisons among multiple groups, and Scheffe's least significant difference (LSD) test for pairs of groups. Significant items were selected, and multiple regression analysis was performed with adjustment of suitable variables.

Results

Eligible participants and baseline characteristics

Background data including physical characteristics for all male participants at baseline are shown in Table 1. Mean weight and height in their fifties, sixties, and seventies, and mean body mass index (BMI) in their seventies were significantly lower than those in their forties ($P < 0.05$).

Among the 200 male participants at baseline, 1 man in his sixties declined to undergo blood and urinary examinations for endogenous hormones. Examinations at baseline were thus performed on 199 men. The second visit, aimed at evaluating changes in BMDs over 3 years, obtained measurements for 181 of the 200 initially recruited participants (90.5%). The following reasons were given for the loss of 19 participants at the 3-year follow-up: 8 men had died, 1 man had moved, 1 man was ill, 4 men declined to participate, and 2 men were away from the area at the time of follow-up. The third visit, aimed at evaluating changes in BMDs over 7 years, evaluated 170 of the 200 initially recruited participants (85%). Loss of 30 participants at the 7-year follow-up was explained as follows: 14 men had died, 3 men had moved, 6 men were ill, 5 men declined to participate, and 2 men were away from the area at the time of follow-up. Among the 200 male participants initially recruited, 153 men participated in the fourth visit held in 2003 (76.5%). Loss of 47 participants at the 10-year follow-up was explained as follows: 33 men had died, 6 men had moved, 4 men were ill, 2 men declined to participate, and 2 men were away from the area at the time of follow-up.

Mean levels of serum concentration of sex steroids at baseline

Age distributions of mean E_2 and FT levels at the initial survey are also shown in Table 1. Because data below the measurable range were excluded from analysis, E_2 and FT data could be obtained for 178 and 198 participants, respectively. Mean serum levels of E_2 and FT were 22.4 and 9.4 pg/ml, respectively. Although no significant age-related trends were seen for E_2, a significant trend toward low values of FT was noted according to age ($P < 0.001$). In addition, mean serum FT was significantly higher for men in their forties than for men in their sixties and seventies ($P < 0.05$).

Predictive capacity of endogenous sex steroids for bone change

Initial mean values and rates of change in L2–L4 BMD over the 3-, 7-, and 10-year periods, classified by age stratum, are shown in Table 2. BMD values at L2–L4 for men had increased slightly by the 10-year follow-up in their fifties and sixties but had decreased a little in the forties and seventies. BMD values at the femoral neck over 10 years had decreased for men in their forties and fifties and had increased considerably in their seventies.

According to multivariate regression analysis using each rate of change for BMD at the lumbar spine over 3, 7, and 10 years as an objective factor and serum levels of E_2 as an explanatory factor after adjusting for age and BMI, beta values for the rate of change for BMD for the first 3, 7, and 10 years were 0.02, 0.04, and –0.02, respectively. Similarly, on multivariate regression analysis using each rate of change for BMD at the femoral neck over 3, 7, and 10 years as an objective factor and serum levels of E_2 as an explanatory factor after adjusting for age and BMI, beta values for the rate of change for BMD for the first 3, 7, and 10 years were –0.07, 0.09, and –0.01, respectively. Total E_2 values could not predict bone change at the lumbar spine or femoral neck at 3, 7, or 10 years.

Again, using the results of multivariate regression analysis to clarify associations between serum FT and

Table 1 Summary characteristics for male participants at baseline classified by age

Birth cohort	Age-group (years)	*n*	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	E2 (pg/mL)		FT (pg/mL)	
			Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
1943–1952	40–49	50	44.2 (2.6)	168.8 (5.2)	69.0 (10.4)	24.2 (3.2)	46	22.1 (7.4)	50	10.9 (2.8)
1933–1942	50–59	50	54.8 (2.7)	165.6 (5.0)[a]	63.5 (9.4)[a]	23.1 (2.9)	43	22.2 (7.0)	50	9.8 (2.6)
1923–1932	60–69	50	64.6 (2.5)	163.0 (4.8)[a]	62.9 (9.6)[a]	23.6 (3.2)	46	23.1 (8.5)	49	8.8 (2.6)[a]
1913–1922	70–79	50	74.0 (2.7)	160.7 (5.4)[a,b]	57.5 (8.3)[a,b,c]	22.2 (2.8)[a]	43	22.3 (7.7)	49	8.2 (3.1)[a]
1913–1952	40–79	200	59.4 (11.4)	164.5 (5.9)	63.2 (10.2)	23.3 (3.1)	178	22.4 (7.6)	198	9.4 (2.9)

BMI body mass index, *E2* total estradiol, *FT* free testosterone, *n* number of participants, *SD* standard deviation

[a] Significantly different ($P < 0.05$) from values of participants in their forties

[b] Significantly different ($P < 0.05$) from values of participants in their fifties

[c] Significantly different ($P < 0.05$) from values of participants in their sixties

Table 2 Mean values (SD) of bone mineral density (g/cm^2) and change rate (%) at lumbar spine L2–L4 and femoral neck over 3, 7, and 10 years, classified by age and gender

Birth cohort	Age-group (years)	L2–L4							Femoral neck				
		Baseline		2nd visit (3-year follow-up)		3rd visit (7-year follow-up)		4th visit (10-year follow-up)	Basesline	2nd visit	3rd visit	4th visit	
		n	BMD (g/cm^2)	*n*	Change rate (%/3 years)	*n*	Change rate (%/7 years)	*n*	Change rate (%/10 years)	BMD (g/cm^2)	Change rate (%/3 years)	Change rate (%/7 years)	Change rate (%/10 years)
1943–1952	40–49	50	1.05 (0.15)	48	0.6 (3.8)	46	−0.6 (5.1)	43	−0.2 (5.8)	0.86 (0.09)	0.3 (4.6)	−1.8 (4.8)	−1.5 (10.9)
1933–1942	50–59	50	0.98 (0.17)	47	1.0 (3.3)	46	−0.0 (6.3)	46	1.6 (8.0)	0.80 (0.13)[a]	−0.2 (4.9)	0.7 (10.0)	−3.0 (6.8)
1923–1932	60–69	50	1.04 (0.21)	49	1.3 (3.6)	47	1.4 (7.1)	41	2.3 (9.4)	0.77 (0.11)[a]	1.0 (7.0)	−0.1 (9.3)	0.3 (12.5)
1913–1922	70–79	50	0.97 (0.19)	37	0.1 (5.3)	31	−1.2 (7.9)	23	−1.5 (9.2)	0.71 (0.08)[a,b,c]	0.9 (6.3)	4.6 (10.2)[a]	6.6 (16.2)[b]
1913–1952	40–79	200	1.01 (0.18)	181	0.8 (4.0)	170	0.0 (6.6)	153	0.8 (8.1)	0.79 (0.12)	0.5 (5.7)	0.5 (8.9)	−0.3 (11.7)

SD standard deviation, *BMD* bone mineral density, *n* number of participants

[a] Significantly different ($P < 0.05$) from values of subjects in their forties

[b] Significantly different ($P < 0.05$) from values of subjects in their fifties

[c] Significantly different ($P < 0.05$) from values of subjects in their sixties

BMD changes at the lumbar spine and femoral neck, beta values of FT for the rate of change for BMD at the lumbar spine at the first 3, 7, and 10 years were 0.08, 0.08, and 0.03, respectively, and those at the femoral neck were 0.21, 0.14, and 0.06, respectively. Mean FT levels were significantly related to the rate of change for BMD at the femoral neck during the first 3 years ($R^2 = 0.05$, $P < 0.01$), but could not predict bone change at any site at 7 or 10 years.

Discussion

The present study examined endogenous hormone levels among men in Japan, measuring changes in BMD over spans of 3, 7, and 10 years. The present study clarified the age distribution of endogenous sex steroids, and a significant trend was seen toward low FT levels with age. FT tended to be significantly lower in the sixties and older when compared with levels in the forties in the present study. Our results support the findings of other reports. Orwoll et al. [26] showed that testosterone levels, particularly FT levels, for 2,623 men 65 years or older were associated with increasing age. Similar findings have been described in other cross-sectional and longitudinal studies [27–29]. Based on these results, we concluded that older men tended to show lower testosterone levels than younger men, similar to the situation with E_2 in women. Some men might display testosterone insufficiency, as seen in women with E_2 insufficiency. However, we do not yet have enough evidence regarding normal ranges in young men and thresholds for testosterone insufficiency. In addition, levels of testosterone may vary among individuals and be influenced by body composition such as adipose tissue, muscle, and bone.

In contrast to testosterone, no significant age-related trend in E_2 was found in the present study. Little information is available regarding E_2 levels in older men. Orwoll et al. [26] reported that E_2 concentrations decreased as age increased, and similar findings have been described in various reports [30–33]. However, other studies have noted stable [34–36] or rising [37] E_2 levels with increasing age. Although the reasons for these discrepancies are unclear, E_2 levels may vary among individuals and may be influenced by body composition such as adipose tissue, muscle, and bone, as well as testosterone.

Regarding the ethnic variations in serum sex steroid levels, as most previous reports have been based on studies of Caucasian men, ethnic variations in FT levels among men remain unclear. To the best of our knowledge, the Osteoporotic Fractures in Men Study (MrOS) is the only study in which a sufficient number of Asian men have participated [26]. For reasons of differences in measurement methods, direct comparison of the present results and

those from the MrOS study is inappropriate, but FT levels among Japanese men tended to be lower than those in MrOS participants, although no significant difference in E_2 levels was apparent. Orwoll et al. [26] analyzed ethnic differences in the MrOS study and stated that FT levels were lower in Asian men than in other races such as Caucasian, African-American, and Hispanic subjects, but no such differences were seen for E_2. The present results support these findings.

The present study found that serum levels of FT could offer a useful predictor of bone loss at the femoral neck within 3 years, but this effect was diluted with longer observation. Regarding the effects of testosterone on bone loss at the hip, Cauley et al. [38] reported, in an epidemiological study of 1,327 men ≥65 years old, that men in the lowest FT category experienced greater hip bone loss over 1.8 years. In addition, Ensrud et al. [39] reported that among men with weight loss, the rate of decline in total hip BMD showed a stepwise increase in magnitude with greater decreases in bioavailable testosterone from baseline. In the present study, the effect of FT levels on bone loss within the relatively short term up to 3 years was observed at the femoral neck, independent of age and BMI, supporting previous reports. Although reasons for site-specific differences in the predictive capacity of FT remain uncertain, we have already reported that bone loss rate differs depending on the site involved in another cohort study [40]. We have also reported that characteristics differ between fast bone losers at the lumbar spine and femoral neck [41]. One reason for site-specific differences might be because degenerative changes that increase BMD, such as osteophytosis or sclerotic change, are observed more frequently at the lumbar spine than at the femoral neck. These results suggest that the predictive capacity of FT might differ according to the sites involved.

A recent study showed that older men with total testosterone or E_2 deficiency were more likely to be osteoporotic [19], but no report evaluated the capacity of serum sex steroids to predict occurrence of OP. Regarding the relationship between testosterone and fracture risk, Mellstrom et al. [42] reported that FT within the normal range was independently associated with the presence, but not occurrence, of osteoporotic fracture in elderly men. In contrast, an analysis from the Rotterdam Study failed to confirm any association between testosterone and fracture risk [43]. Data from the Framingham study indicated that men with low serum testosterone and E_2 levels were at increased risk for incident hip fractures [44]. A recent report from the Dubbo osteoporosis epidemiology study revealed that in men older than 60 years, serum testosterone is independently associated with the risk of osteoporotic fracture [45]. We also tried to evaluate the predictive capacity of serum levels of sex steroids and occurrence of OP based on WHO criteria [46] and osteoporotic fractures, but only identified 7 cases of OP and 10 cases of osteoporotic fractures including 1 vertebral fracture, 1 hip fracture, 2 wrist fractures, 3 costal fractures, 2 ankle fractures, and 1 finger fracture. After analysis using Cox proportional hazards models adjusted for age and BMI, serum levels of FT were significantly related to incidence of OP (hazard ratio, 0.42; 95% confidence interval, 0.19–0.90), but not to incidence of osteoporotic fractures. This analysis suggests the possibility of serum FT as a predictor for OP occurrence over 10 years. However, the number of occurrences of OP seems to be too small to reach any conclusion regarding the presence or absence of associations between sex steroids and OP or osteoporotic fractures.

There are several limitations in the present study. First, the small sample size seemed to be the most severe weakness. In fact, as already noted, only 7 cases of OP and 10 cases of osteoporotic fractures were accumulated during the 10 years of the study. Longer observation in the present cohort might be required to confirm the association between sex steroids and OP or osteoporotic fracture. Second, the dropout rate over 10 years for patients in their seventies was considerably high (54.0%). This high dropout rate might cause bias. In fact, the tendency toward an increase in BMD at the femoral neck for patients in their seventies was skewed by withdrawal bias. On the basis of this hypothesis, we reanalyzed the multivariate regression analysis to assess the change rate of BMD at the femoral neck and serum FT with exclusion of subjects in their seventies. However, the results were similar, with serum levels of FT predicting bone loss at the femoral neck within 3 years (beta = 0.17, $P = 0.05$), but diluted effects with longer observation (7 years: beta = 0.8, $P = 0.38$; 10 years: beta = 0.03, $P = 0.77$). Third, all serum samples were extracted between 0900 and 1500, not at a fixed time in the morning, although samples for measurement of FT are recommended to be collected in the morning. Serum levels of testosterone tend to increase toward night, peaking in the early morning, then decreasing rapidly and reaching a nadir between 1300 and 2300. We collected samples when FT levels would probably have been decreasing toward the nadir. The present study might thus have underestimated FT values compared to collection at a fixed time in the morning.

Conversely, the study design shows several notable strengths. In this population-based cohort study, subjects were selected randomly from the resident registration list. BMD was carefully measured by a single observer (N.Y.), and measurements were repeated 3, 7, and 10 years later with high participation rate by the same device and same observer. Another strength was that the effect of serum levels of sex steroids on changes in BMD could be estimated directly.

In conclusion, we clarified that serum levels of FT could predict bone loss within 3 years, but not longer. Further observations are required to confirm the relationship between FT, E_2, and spinal OP and osteoporotic fractures. Other environmental and genetic factors should also be evaluated to develop strategies for the early prevention of OP.

Acknowledgments This work was supported by Grants-in-Aid for Scientific Research: B20390182 (Noriko Yoshimura), C20591737 (Toru Akune), C20591774 (Shigeyuki Muraki), and Young Scientists A18689031 (Hiroyuki Oka) and Collaborating Research with NSF 08033011-00262 (Director, Noriko Yoshimura) from the Ministry of Education, Culture, Sports, Science and Technology, H17-Men-eki-009 (Director, Kozo Nakamura), H18-Choujyu-037 (Director, Toshitaka Nakamura) and H20-Choujyu-009 (Director, Noriko Yoshimura) from the Ministry of Health, Labour and Welfare in Japan. This study was also supported by grants from the Japan Osteoporosis Society (Noriko Yoshimura), Nakatomi Foundation (Noriko Yoshimura) and research aid from the Japanese Orthopaedic Association (JOA-Subsidized Science Project Research 2006-1, Director, Hiroshi Kawaguchi). The sponsors played no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The authors thank Mrs. Tamako Tsutsumi, Mrs. Kanami Maeda, and other members in the Public Office in Taiji Town and members of the Public Health Center in Shingu City for their assistance in the location and scheduling of participants for examinations.

Conflict of interest statement The authors have no conflicts/disclosures to declare regarding the present manuscript.

References

1. Jornell O, Kanis JA, Oden A, Sembo I, Redlund-Johnell I, Petterson C, De Laet C, Jonsson B (2004) Mortality after osteoporotic fractures. Osteoporosis Int 15:38–42
2. Muraki S, Yamamoto S, Ishibashi H, Nakamura K (2006) Factors associated with mortality following hip fracture in Japan. J Bone Miner Metab 24:100–104
3. Yoshimura N, Muraki S, Oka H, Mabuchi A, En-yo Y, Yoshida M, Saika A, Suzuki T, Yoshida H, Kawaguchi H, Nakamura K, Akune T (2009) Prevalence of knee osteoarthritis, lumbar spondylosis and osteoporosis in Japanese men and women: the research on osteoarthritis/osteoporosis against disability study. J Bone Miner Metab 27:620–628
4. Sakata T, Yaegashi Y, Hosoi T, Orimo H (2009) The 2007 nationwide survey on the incidence of hip fracture in Japan and 20-year trends. Osteoporos Int 20(suppl 1):S63
5. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA (1999) Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet 353:878–882
6. Seeman E (2004) Osteoporosis in men. In: Seeman E (ed) Invest in your bones. International Osteoporosis Foundation, Nyon, Switzerland, pp 1–16
7. Amin S, Felson DT (2001) Osteoporosis in men. Rheum Dis Clin N Am 27:19–47
8. Forsen L, Sogaard AJ, Meyer HE, Edna T, Kopjar B (1999) Survival after hip fracture, short- and long-term excess mortality according to age and gender. Osteoporos Int 10:73–78
9. Riis BJ, Rodbro P, Christiansen D (1986) The role of serum concentrations of sex steroids and bone turnover in the development and occurrence of postmenopausal osteoporosis. Calcif Tissue Int 38:318–322
10. Slemenda C, Hui SL, Longscope C, Johnston CC (1987) Sex steroids and bone mass: a study of changes about the time of menopause. J Clin Invest 80:1261–1269
11. Slemenda C, Longscope C, Peacock M, Hui S, Johnston CC (1996) Sex steroids, bone mass and bone loss. J Clin Invest 97:14–21
12. Yoshimura N, Kasamatsu T, Sakata K, Hashimoto T, Cooper C (2002) The relationship between endogenous estrogen, sex hormone binding globulin and bone loss in female residents of a rural Japanese community: the Taiji study. J Bone Miner Metab 20:303–310
13. Ettinger B, Pressman A, Sklarin P, Bauer D, Cauley JA, Cummings SR (1998) Associations between low levels of serum estradiol, bone density, and fractures among elderly women: the study of osteoporotic fractures. J Clin Endocrinol Metab 83:2239–2243
14. Stone K, Bauer DC, Black DM, Sklarin P, Ensrud KE, Cummings SR (1998) Hormonal predictors of bone loss in elderly women: a prospective study. J Bone Miner Res 13:1167–1174
15. Cummings SR, Browner WS, Bauer DB, Stone K, Ensrud K, Jamal S, Ettinger B (1998) Endogenous hormones and the risk of hip and vertebral fractures among older women. N Engl J Med 339:733–738
16. Murphy S, Khaw KT, Cassidy A, Compston JE (1993) Sex hormones and bone mineral density in elderly men. Bone Miner 20:133–140
17. Ongphiphadhanakul B, Rajatanavin R, Chailurkit L, Piaseu N, Teerarungsikul K, Sirisriro R, Komindr S, Puavilai G (1995) Serum testosterone and its relation to bone mineral density and body composition in normal males. Clin Endocrinol (Oxf) 43:727–733
18. Rucker D, Ezzat S, Diamandi A, Khosravi J, Hanley DA (2004) IGF-I and testosterone levels as predictors of bone mineral density in healthy, community-dwelling men. Clin Endocrinol (Oxf) 60:491–499
19. Fink HA, Ewing SK, Ensrud KE, Barrett-Connor E, Taylor BC, Cauley JA, Orwoll ES (2006) Association of testosterone and estradiol deficiency with osteoporosis and rapid bone loss in older men. J Clin Endocrinol Metab 91:3908–3915
20. Van Pottelbergh I, Goemaere S, Kaufman JM (2003) Bioavailable estradiol and an aromatase gene polymorphism are determinants of bone mineral density changes in men over 70 years of age. J Clin Endocrinol Metab 88:3075–3081
21. Gennari L, Merlotti D, Martini G, Gonnelli S, Franci B, Campagna S, Lucani B, Dal Canto N, Valenti R, Gennari C, Nuti R (2003) Longitudinal association between sex hormone levels, bone loss, and bone turnover in elderly men. J Clin Endocrinol 88:5327–5333
22. Kasamatsu T, Yoshimura N, Morioka S, Sugita K, Hashimoto T (1996) A population survey on bone mineral density in a fishing village in Wakayama Prefecture (Part 1). Distribution of bone mineral density by sex and age on a representative sample of the community. Jpn J Hyg 50:1084–1092 (in Japanese)
23. Yoshimura N, Kasamatsu T, Morioka S, Hashimoto T (1996) A population survey on bone mineral density in a fishing village in Wakayama Prefecture (Part 2). The analysis of the risk factors affecting the bone mineral density. Jpn J Hyg 51:677–684 (in Japanese)
24. 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
25. 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 (DPX-L). J Wakayama Med Soc 48:461–466
26. Orwoll E, Lambert LC, Marshall LM, Phipps K, Blank J, Barrett-Connor E, Cauley J, Ensrud K, Cummings S (2006) Testosterone and estradiol among older men. J Clin Endocrinol Metab 91:1336–1344
27. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR, Baltimore Longitudinal Study of Aging (2001) Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 86:724–731
28. Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB (2002) Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab 87:589–598
29. Liu PY, Beilin J, Meier C, Nguyen TV, Center JR, Leedman PJ, Seibel MJ, Eisman JA, Handelsman DJ (2007) Age-related changes in serum testosterone and sex hormone binding globulin in Australian men: longitudinal analyses of two geographically separate regional cohorts. J Clin Endocrinol Metab 92:3599–3603
30. Khosla S, Melton LJ, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL (1998) Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. J Clin Endocrinol Metab 83:2266–2274
31. Khosla S, Melton J III, Atkinson EJ, O'Fallon WM (2001) Relationship of serum sex steroid levels to longitudinal changes in bone density in young versus elderly men. J Clin Endocrinol Metab 86:3555–3561
32. van den Beld AW, de Jong FH, Grobbee DE, Pols HA, Lamberts SW (2000) Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density, and body composition in elderly men. J Clin Endocrinol Metab 85:3276–3282
33. Leifke E, Gorenoi V, Wichers C, Von Zur Muhlen A, Von Buren E, Brabant G (2000) Age-related changes of serum sex hormones, insulin-like growth factor-1 and sex-hormone binding globulin levels in men: cross-sectional data from a healthy male cohort. Clin Endocrinol (Oxf) 53:689–695
34. Gray A, Feldman HA, McKinlay JB, Longcope C (1991) Age, disease and changing sex hormone levels in middle-aged men: results of the Massachusetts male aging study. J Clin Endocrinol Metab 73:1016–1025
35. Muller M, den Tonkelaar I, Thijssen JH, Grobbee DE, van der Schouw YT (2003) Endogenous sex hormones in men aged 40–80 years. Eur J Endocrinol 149:583–589
36. Belanger A, Candas B, Dupont A, Cusan L, Diamond P, Gomez JL, Labrie F (1994) Changes in serum concentrations of conjugated and unconjugated steroids in 40- to 80-year-old men. J Clin Endocrinol Metab 79:1086–1090
37. Bjornerem A, Straume B, Midtby M, Fonnebo V, Sundsfjord J, Svartberg J, Acharya G, Oian P, Berntsen GK (2004) Endogenous sex hormones in relation to age, sex, lifestyle factors, and chronic diseases in a general population: the Tromso Study. J Clin Endocrinol Metab 89:6039–6047
38. Cauley J, Taylor B, Fink H, Ensrud K, Bauer D, Barrett-Connor E, Marshall L, Nevitt M, Stefanick M, Orwoll E (2004) Sex steroid hormones in older men: cross-sectional and longitudinal associations with bone mineral density (BMD). The Osteoporotic Fracture in Men Study (MrOS). J Bone Miner Res 19(suppl 1):S16
39. Ensrud KE, Lewis CE, Lambert LC, Taylor BC, Fink HA, Barrett-Connor E, Cauley JA, Stefanick ML, Orwoll E, Osteoporotic Fractures in Men MrOS Study Research Group (2006) Endogenous sex steroids weight change and rates of hip bone loss in older men: the MrOS study. Osteoporos Int 17:1329–1336
40. 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
41. Yoshimura N, Takijiri T, Kinoshita H, Danjoh S, Kasamatsu T, Morioka S, Sakata K, Hashimoto T, Takeshita T (2004) Characteristics and course of bone mineral densities among fast bone losers in a rural Japanese community: the Miyama study. Osteoporos Int 15:139–144
42. Mellström D, Johnell O, Ljunggren O, Eriksson AL, Lorentzon M, Mallmin H, Holmberg A, Redlund-Johnell I, Orwoll E, Ohlsson C (2006) Free testosterone is an independent predictor of BMD and prevalent fractures in elderly men: MrOS Sweden. J Bone Miner Res 21:529–535
43. Goderie-Plomp HW, van der Klift M, de Ronde W, Hofman A, de Jong FH, Pols HA (2004) Endogenous sex hormones, sex hormone-binding globulin, and the risk of incident vertebral fractures in elderly men and women: the Rotterdam Study. J Clin Endocrinol Metab 89:3261–3269
44. Amin S, Zhang Y, Felson DT, Sawin CT, Hannan MT, Wilson PW, Kiel DP (2006) Estradiol, testosterone, and the risk for hip fractures in elderly men from the Framingham Study. Am J Med 119:426–433
45. Meier C, Nguyen TV, Handelsman DJ, Schindler C, Kushnir MM, Rockwood AL, Meikle AW, Center JR, Eisman JA, Seibel MJ (2008) Endogenous sex hormones and incident fracture risk in older men: the Dubbo Osteoporosis Epidemiology Study. Arch Intern Med 168:47–54
46. World Health Organization (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. WHO Technical Report Series 843. WHO, Geneva

Osteoarthritis and Cartilage 18 (2010) 1227–1234

Osteoarthritis and Cartilage

Association of radiographic and symptomatic knee osteoarthritis with health-related quality of life in a population-based cohort study in Japan: the ROAD study

S. Muraki †*, T. Akune †, H. Oka ‡, Y. En-yo §, M. Yoshida §, A. Saika §, T. Suzuki ||, H. Yoshida ||, H. Ishibashi ||, F. Tokimura ||, S. Yamamoto ||, K. Nakamura ¶, H. Kawaguchi ¶, N. Yoshimura ‡

† *Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, Faculty of Medicine, The University of Tokyo, Tokyo, Japan*
‡ *Department of Joint Disease Research, 22nd Century Medical and Research Center, Faculty of Medicine, The University of Tokyo, Tokyo, Japan*
§ *Department of Orthopaedic Surgery, Wakayama Medical University, Wakayama, Japan*
|| *Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan*
¶ *Department of Sensory & Motor System Medicine, Faculty of Medicine, The University of Tokyo, Tokyo, Japan*

ARTICLE INFO

Article history:
Received 4 August 2009
Accepted 17 June 2010

Keywords:
Osteoarthritis
Knee
Quality of life
Cohort
Epidemiology

SUMMARY

Objective: Knee osteoarthritis (OA) is a major public health issue causing chronic pain and disability. However, there is little information on the impact of this disease on quality of life (QOL) in Japanese men and women. The objective of the present study was to clarify the impact of radiographic and symptomatic knee OA on QOL in Japan.

Methods: This study examined the association of radiographic and symptomatic knee OA with QOL parameters such as the Medical Outcomes Study Short Form-8 (SF-8), EuroQOL (EQ-5D) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Radiographic knee OA was defined according to Kellgren/Lawrence (KL) grades, and symptomatic knee OA was defined as KL = 3 or 4 with knee pain. We also examined the independent association of symptomatic knee OA and grip strength with QOL.

Results: From the 3040 participants in the Research on Osteoarthritis Against Disability (ROAD) study, the present study analyzed 2126 subjects older than 40 years who completed the questionnaires (767 men and 1359 women; mean age, 68.9 ± 10.9 years). Subjects with KL = 3 or 4 had significantly lower physical QOL as measured by the physical component summary (PCS) score of the SF-8 and pain domains of the WOMAC, whereas mental QOL, as measured by the mental component summary (MCS) score of the SF-8, was higher in subjects with KL = 3 or 4 than KL = 0 or 1. Symptomatic knee OA was significantly more likely than radiographic knee OA without pain to be associated with physical QOL loss as measured by the PCS score and physical domains of the WOMAC. Symptomatic knee OA and grip strength were independently associated with physical QOL.

Conclusion: This cross-sectional study revealed that subjects with symptomatic knee OA had significantly lower physical QOL than subjects without it.

Introduction

Knee osteoarthritis (OA) is a major public health issue that causes chronic pain and disability[1–3]. The prevalence of radiographic knee OA is high in Japan[4], with 25,300,000 subjects aged 40 years and older estimated to experience radiographic knee OA[5]. According to the recent National Livelihood Survey of the Ministry of Health, Labour and Welfare in Japan, OA is ranked fourth among diseases that cause disabilities that subsequently require support with activities of daily living[6].

Quality of life (QOL) measurements in patients with chronic diseases are useful tools for estimating disease impact; these QOL scales may be generic or disease specific. Among the generic scales, the EuroQOL (EQ-5D) has been widely used to measure health-related QOL (HRQOL) in patients with OA[7,8], and several studies have used the Medical Outcomes Study Short Form-36 (SF-36) in

* Address correspondence and reprint requests to: Shigeyuki Muraki, Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, Faculty of Medicine, The University of Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113-8655, Japan. Tel: 81-3-5800-9178; Fax: 81-3-5800-9179.
E-mail address: murakis-ort@h.u-tokyo.ac.jp (S. Muraki).

1063-4584/$ – see front matter © 2010 Osteoarthritis Research Society International. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.joca.2010.06.001

Caucasian patients with OA[9–11]. However, almost all of these studies include only patients with knee OA, and there are few population-based studies regarding knee OA and QOL[11]. A previous population-based study in Caucasians showed that arthritis has a major impact on the HRQOL measured by the SF-36 in a community setting[11], although arthritis was examined by self-reported means and not by radiographs. In terms of disease-specific scales for knee OA, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) has been used for Caucasians[12] and Asians[13,14], although these reports were not population-based studies. Furthermore, there is little information on the impact of knee OA with QOL in Japan, although a population survey suggests that the disease pattern differs among races[15–17]. In fact, the prevalence of knee OA in Japan[4] was much higher than that of previous epidemiologic studies in elderly Caucasians[16,18]. Furthermore, in terms of risk factors, studies in Caucasians have suggested that occupational activities that include kneeling and squatting were associated with knee OA[19], whereas these activities were not associated with Kellgren/Lawrence (KL) grades ≥ 2 OA in our previous study in Japan[20]. Therefore, the impact of knee OA on QOL also appears to differ in different populations. It would thus be of interest to clarify the impact of OA on QOL in a Japanese population.

The principal clinical symptom of knee OA is pain[21], but the correlation with the radiographic severity of knee OA is controversial[4,22–24]. Thus it would be interesting to determine whether the impact of radiographic knee OA on QOL differs according to the severity of OA. Furthermore, pain is strongly associated with QOL, so it would be of interest to clarify the impact of symptomatic OA as well as radiographic knee OA on QOL.

Gender differences have also been observed in knee OA. The prevalence of knee OA is higher in women than men[4], and the association of knee pain with knee OA also differs by gender[4]. Thus, the impact of these diseases on QOL may also differ between genders. However, to the best of our knowledge, there are no population-based studies that assess the association of knee OA with QOL in men and women separately.

Grip strength is a useful marker of muscle function and sarcopenia[25]. There is growing evidence that reduced grip strength is associated with adverse outcomes including morbidity[26], disability[27], falls[27], higher fracture rates[28], increased length of hospital stay[29], and mortality[27]. A previous study also showed that grip strength is related to total muscle strength[30]. Furthermore, there is increasing recognition that grip strength is a useful clinical marker of sarcopenia, and recent work has validated this approach, demonstrating that grip strength is more strongly associated with age and is a better predictor of poor mobility than other potential markers such as calf muscle area[31]. Previous reports have shown that low muscle mass was also associated with reduced QOL[32,33]; thus, the association of knee OA with QOL may be influenced by grip strength, but again, no studies have examined the association of knee OA and grip strength with QOL simultaneously in the same population.

The first objective of this study is to clarify the association of radiographic severity of knee OA with QOL among Japanese men and women using the large-scale, population-based cohort study called the Research on Osteoarthritis Against Disability (ROAD). Because pain is strongly associated with QOL, we also examined the association of symptomatic knee OA with QOL. Finally, we analyzed the independent associations of knee OA and grip strength with QOL.

Subjects and methods

Subjects

The ROAD study is a nationwide prospective study designed to establish epidemiologic indexes for evaluation of clinical evidence for the development of a disease-modifying treatment for bone and joint diseases (with OA and osteoporosis as the representative bone and joint diseases). It consists of population-based cohorts in several communities in Japan. A detailed profile of the ROAD study has been described in detail elsewhere[4,5,34]; a brief summary is provided here. To date, we have completed creation of a baseline database including clinical and genetic information for 3040 inhabitants (1061 men and 1979 women) ranging in age from 23 to 95 years (mean, 70.6 years), who were recruited from resident registration listings in three communities: an urban region in Itabashi, Tokyo, a mountainous region in Hidakagawa, Wakayama, and a seacoast region in Taiji, Wakayama. All participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology. Anthropometric measurements included height and weight, and body mass index (BMI) (weight [kg]/height^2 [m^2]) was calculated. Grip strength was measured on bilateral sides using a TOEI LIGHT handgrip dynamometer (TOEI LIGHT Co., Ltd, Saitama, Japan), and the better measurement was used to characterize maximum muscle strength. Among 2995 subjects aged 40 years or older in the ROAD study, 2243 (74.9%), 2245 (75.0%) and 2222 (74.2%) subjects completed the SF-8, the EQ-5D and the WOMAC, respectively, and 2126 (71.0%) subjects completed all three questionnaires. The present study analyzed 2126 subjects (767 men and 1359 women) aged 40 years (mean, 68.9 $\pm$ 10.9 years) or older who had completed the SF-8, the EQ-5D, and the WOMAC.

Radiographic assessment

All participants had radiographic examination of both knees using anterior–posterior and lateral views with weight-bearing and foot map positioning. Knee radiographs were read without knowledge of participant clinical status by a single well-experienced orthopaedist (SM) using the KL radiographic atlas for overall knee radiographic grades[35]. In KL grade, radiographs are scored as grade 0 through 4, with higher grades being associated with more severe OA. The higher KL grade in both knees was designated as that of the participant. Symptomatic knee OA was defined as: (1) a subject reporting knee pain lasting at least 1 month with pain having last occurred within the current or previous year; and (2) KL = 3 or 4 OA in the painful knee. To evaluate the intra-observer variability of KL grading, 100 randomly selected radiographs of the knee were scored by the same observer more than 1 month after the first reading. One hundred other radiographs were also scored by two experienced orthopaedic surgeons (SM & HO) using the same atlas for inter-observer variability. The evaluated intra- and inter-observer variabilities were confirmed by kappa analysis to be sufficient for assessment (0.86 and 0.80, respectively).

Instruments

The SF-8 generates a health profile consisting of eight scales and two summary measures describing HRQOL. The SF-8 is an alternate form to the SF-36, which is the most widely used patient-based health status survey, translated into more than 40 languages; the Japanese version of the SF-36 has been well validated[36]. The SF-8 uses a single question to measure each of the eight SF-36 domains. In the SF-8, each of the eight items assesses a different dimension of health: General Health (GH), Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), Vitality (VT), Social Functioning (SF), Mental Health (MH) and Role Emotional (RE). The SF-8 was scored by assigning the mean SF-36 scale score from the 2002 general Japanese population to each response category of the SF-8 measuring the same concept, and then weighting each SF-8 item to

compute aggregate physical component summary (PCS) and mental component summary (MCS) scores. The SF-8 may be scored using a published algorithm for Japanese versions of the SF-8, which has been well validated[37]. The EQ-5D self-report questionnaire measures five domains of HRQOL, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression[38]. Each of the five domains is assessed by a single question with three response levels (no problem, some problems, and extreme problems), so the EQ-5D defines a total of 243 health states. These results were coded and converted to a score of utility using the tables of values[39]. The EQ-5D scoring algorithm was first developed using time trade off-based preference scores for a sample of these health states from a representative sample of the UK general population[38]; the Japanese version of the EQ-5D has been validated[39]. This EQ-5D algorithm is used worldwide and generates scores ranging from −0.111 to 1.000, with negative scores representing health states worse than being dead, 0 representing being dead, and 1.00 representing a state of full health. The WOMAC, a 24-item OA-specific index, consists of three domains: pain, stiffness, and physical function. Each of these 24 items is graded on either a five-point Likert scale or a 100-mm visual analogue scale[12,40]. In the present study, we used the Likert scale (version LK 3.0). The domain score ranges from 0 to 20 for pain, 0 to 8 for stiffness, and 0 to 68 for physical function. Japanese versions of the WOMAC have also been validated[41].

Statistical analysis

The differences in age, height, weight, BMI, grip strength, and QOL measurements between men and women were examined by the Student's *t* test. The prevalence of radiographic and symptomatic knee OA was compared between men and women using the chi-square test. We also used the chi-square test to analyze whether subjects with one symptomatic knee were likely to have symptomatic OA in the other knee. According to KL grade[35], KL = 2 was defined as definite osteophytosis but no definite joint space narrowing, and KL = 3 and 4 included definite joint space narrowing. We thus categorized KL grade in KL = 0 or 1, KL = 2, or KL = 3 or 4, and differences among each KL grade with QOL measurements were determined using the Tukey Honestly Significant Difference (HSD) test without adjustment and after adjustment for age, BMI, and grip strength in men and women. We further classified subjects into those with symptomatic knee OA, those with KL = 3 or 4 knee OA without pain, and those without KL = 3 or 4 knee OA, and compared their association with QOL using the Tukey HSD test after adjustment for age, BMI, and grip strength. To determine the independent association of symptomatic knee OA and grip strength with QOL, we used multiple regression analysis without adjustment and after adjustment for age and BMI. Data analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC).

Results

The characteristics of the 2126 participants in the present study are shown in Table I. The prevalence of knee OA was significantly higher in women than men. The prevalence of bilateral and unilateral symptomatic knee OA was 2.0% and 3.0% in men, and 5.6% and 5.8% in women, respectively. Chi-square test showed that when the right knee had symptomatic knee OA, the odds ratio for the left knee to have symptomatic knee OA was 86.3 and 59.7 in men and women, respectively. The PCS and MCS of the SF-8 and the EQ-5D utility scores were significantly higher and the all domains of WOMAC were significantly lower in men than women, indicating that the QOL scores were higher in men than women.

Table I
Characteristics of participants

	Overall	Men	Women	*P*-Values
Number of subjects	2126	767	1359	
Age, years	68.9 ± 10.9	69.7 ± 10.5	68.4 ± 11.1	0.006
Height, cm	154.6 ± 9.2	162.8 ± 6.7	150.0 ± 6.9	<0.0001
Weight, kg	55.0 ± 10.9	61.5 ± 10.8	51.4 ± 9.0	<0.0001
BMI, kg/m^2	22.9 ± 3.6	23.1 ± 3.4	22.8 ± 3.7	0.03
Grip strength, kg	25.5 ± 9.3	33.2 ± 8.9	21.2 ± 6.3	<0.0001
Radiographic knee OA, %	17.9	11.6	21.5	<0.0001
Symptomatic knee OA, %	9.0	5.0	11.3	<0.0001
SF-8				
PCS	47.0 ± 7.0	47.4 ± 6.8	46.8 ± 7.0	0.03
MCS	52.8 ± 5.9	53.4 ± 5.3	52.5 ± 6.1	0.0009
EQ-5D	0.90 ± 0.15	0.91 ± 0.14	0.90 ± 0.15	0.03
WOMAC				
Pain (0–20)	1.37 ± 2.44	1.13 ± 2.16	1.50 ± 2.57	0.0003
Stiffness (0–8)	0.71 ± 1.25	0.63 ± 1.09	0.77 ± 1.33	0.01
Function (0–68)	4.08 ± 7.93	3.35 ± 7.06	4.49 ± 8.37	0.001

Except where otherwise indicated, values are the mean ± SD.
The differences between men and women were examined by the Student's *t* test except for the prevalence of radiographic and symptomatic knee OA.
The prevalence of radiographic and symptomatic knee OA was compared between men and women using the chi-square test.
Radiographic knee OA was defined as KL grade 3 or 4.
Symptomatic knee OA was defined as KL grade 3 or 4 with knee pain.
SF-8, Medical Outcomes Study Short Form-8.

The scores for PCS and MCS in the SF-8, the EQ-5D utility scores, and all domains in the WOMAC by KL grade of knee OA in men and women are shown in Tables II and III. The associations of age, BMI, and grip strength with each QOL parameter were significant in men and women by linear regression analysis ($P < 0.01$), except for the association of age with the MCS of the SF-8. Thus, we used the Tukey HSD test after adjustment for age, BMI, and grip strength to determine the association of radiographic severity of knee OA with QOL. Men and women with KL = 3 or 4 had significantly lower QOL measured by PCS of the SF-8 and pain domains of the WOMAC than those with KL = 0 or 1 as well as KL = 2. In addition, the MCS scores were higher in men and women with KL = 3 or 4 compared with KL = 0 or 1. The EQ-5D utility scores were not significantly associated with the KL grade of the knee after adjustment for age, BMI and grip strength.

Next, to determine impact of symptoms of radiographic knee OA with QOL, we classified subjects into those with symptomatic knee OA, defined as KL = 3 or 4 with knee pain, those with KL = 3 or 4 without pain, and those without KL = 3 or 4 and compared the impact of each type of OA on QOL using the Tukey HSD test after adjustment for age, BMI, and grip strength (Fig. 1). In men and women, PCS of the SF-8 and physical function domain of the WOMAC were significantly lower in subjects with symptomatic knee OA compared with those without KL = 3 or 4 knee OA (men: difference in mean −5.9, 95% CI −8.6 to −3.2 and difference in mean 4.9, 95% CI 2.2 to 7.6, respectively; women: difference in mean −4.3, 95% CI −5.7 to −2.9 and difference in mean 3.9, 95% CI 2.3 to 5.5, respectively) as well as KL = 3 or 4 knee OA without pain (men: difference in mean −6.3, 95% CI −9.7 to −3.0 and difference in mean 5.7, 95% CI 2.3 to 9.1, respectively; women: difference in mean −4.9, 95% CI −6.7 to −3.1 and difference in mean 3.9, 95% CI 1.8 to 5.9, respectively), whereas among those with KL = 3 or 4 knee OA without pain and no KL = 3 or 4 knee OA, there were no significant differences in PCS of the SF-8 and physical function domain of the WOMAC. In women, MCS of the SF-8 was significantly higher in subjects with symptomatic knee OA compared with those without KL = 3 or 4 knee OA (difference in mean 2.6, 95% CI 1.3 to 4.0) as well as KL = 3 or 4 knee OA without pain (difference in mean 2.3, 95% CI 0.6 to 4.0). The EQ-5D utility score was

Table II
Mean scores of the SF-8, EQ-5D, and WOMAC scales by KL grade in men

		Severity of knee OA			Difference in means (95% CI)	
		KL = 0 or 1 (n = 444)	KL = 2 (n = 231)	KL = 3 or 4 (n = 92)	KL = 3 or 4 vs KL = 0 or 1	KL = 3 or 4 vs KL = 2
SF-8						
PCS	Crude	48.1 ± 0.3	47.1 ± 0.4	44.7 ± 0.7	−3.3 (−5.2, −1.5)	−2.3 (−4.3, −0.4)
	Adjusted	47.8 ± 0.3	47.4 ± 0.4	45.5 ± 0.7	−2.3 (−4.2, −0.5)	−1.9 (−3.9, 0.0)
MCS	Crude	52.8 ± 0.2	53.7 ± 0.3	55.3 ± 0.5	2.5 (1.1, 3.9)	1.6 (0.1, 3.1)
	Adjusted	52.9 ± 0.3	53.7 ± 0.4	55.2 ± 0.6	2.3 (0.8, 3.8)	1.5 (−0.02, 3.1)
EQ-5D	Crude	0.92 ± 0.01	0.91 ± 0.01	0.87 ± 0.01	−0.06 (−0.10, −0.02)	−0.04 (−0.08, 0.00)
	Adjusted	0.92 ± 0.01	0.91 ± 0.01	0.89 ± 0.01	−0.03 (−0.07, 0.01)	−0.03 (−0.07, 0.01)
WOMAC						
Pain	Crude	0.92 ± 0.10	1.13 ± 0.14	2.11 ± 0.22	1.19 (0.61, 1.76)	0.97 (0.36, 1.59)
	Adjusted	1.03 ± 0.10	1.02 ± 0.14	1.75 ± 0.22	0.72 (0.14, 1.30)	0.73 (0.12, 1.34)
Stiffness	Crude	0.57 ± 0.05	0.65 ± 0.07	0.91 ± 0.11	0.34 (0.05, 0.64)	0.26 (0.05, 0.58)
	Adjusted	0.60 ± 0.05	0.61 ± 0.07	0.80 ± 0.12	0.20 (−0.10, 0.50)	0.19 (0.13, 0.51)
Function	Crude	2.83 ± 0.33	3.38 ± 0.46	6.08 ± 0.73	3.24 (1.36, 5.12)	2.70 (0.67, 4.73)
	Adjusted	3.31 ± 0.32	2.88 ± 0.45	4.66 ± 0.72	1.35 (−0.53, 3.23)	1.77 (−0.19, 3.74)

Values are mean ± standard error (SE). SF-8, Medical Outcomes Study Short Form-8.
Adjusted differences in means were calculated by Tukey HSD test after adjustment for age, BMI and grip strength.

significantly lower in subjects with symptomatic knee OA compared with those without KL = 3 or 4 knee OA (difference in mean −0.08, 95% CI −0.13 to −0.02) as well as KL = 3 or 4 knee OA without pain in men (difference in mean −0.08, 95% CI −0.15 to −0.01), but not in women.

Next, to examine the independent association of symptomatic knee OA and grip strength on QOL, multiple regression analysis was used with age, BMI, grip strength, and the presence of symptomatic knee OA as independent variables (Table IV). In men and women, symptomatic knee OA and grip strength were independently associated with PCS of the SF-8 (R^2, 0.11 and 0.17, respectively), EQ-5D utility scores (R^2, 0.08 and 0.12, respectively), and pain (R^2, 0.12 and 0.16, respectively), stiffness (R^2, 0.06 and 0.09, respectively) and physical function domains (R^2, 0.13 and 0.21, respectively) of the WOMAC.

Discussion

This is the first study to examine the association of radiographic and symptomatic knee OA with QOL measured by generic scales such as the SF-8, which is an alternate form of the SF-36, and the EQ-5D, as well as a disease-specific scale such as WOMAC in Japanese men and women using a large-scale population-based cohort study. In the present study, subjects with KL = 3 or 4 had significantly lower physical QOL than those with KL = 0 or 1 as well as KL = 2. At the same time, the MCS scores were higher in KL = 3 or 4 than KL = 0 or 1 in men and women. Furthermore, symptomatic knee OA was significantly associated with lower physical QOL compared with radiographic knee OA without pain. We further clarified the independent associations with symptomatic knee OA and grip strength. Symptomatic knee OA and grip strength were independently associated with lower QOL.

In the present study, physical QOL was significantly lower in subjects with KL = 3 or 4 compared with KL = 0 or 1 as well as KL = 2 in men and women. Samsa *et al.* reviewed the existing literature and concluded that the Minimally Clinically Important Difference (MCID) for the SF-36 is typically in the range of 3–5 points[42], implying that differences in SF-36 scores of 1–2 points are not important, but differences in scores of 3 points or more are clinically important. In this study, differences of PCS scores between subjects with KL = 3 or 4 and those with KL = 0 or 1 were 3.4 and 4.6 in men and women, respectively. The differences were similar to MCID thresholds, indicating that KL = 3 or 4 knee OA may be clinically important for physical QOL. A previous study in China

Table III
Mean scores of the SF-8, EQ-5D, and WOMAC scales by KL grade in women

		Severity of knee OA			Difference in means (95% CI)	
		KL = 0 or 1 (N = 541)	KL = 2 (N = 526)	KL = 3 or 4 (N = 292)	KL = v3 or 4 vs KL = 0 or 1	KL = 3 or 4 vs KL = 2
SF-8						
PCS	Crude	48.4 ± 0.3	46.9 ± 0.3	43.8 ± 0.4	−4.5 (−5.7, −3.4)	−3.0 (−4.2, −1.9)
	Adjusted	47.1 ± 0.3	47.4 ± 0.3	45.5 ± 0.4	−1.6 (−2.9, −0.3)	−1.9 (−3.1, −0.7)
MCS	Crude	52.1 ± 0.3	52.3 ± 0.3	53.8 ± 0.4	1.7 (0.7, 2.7)	1.4 (0.4, 1.5)
	Adjusted	51.9 ± 0.3	52.5 ± 0.3	53.8 ± 0.4	1.9 (0.7, 3.1)	1.3 (0.2, 2.4)
EQ-5D	Crude	0.92 ± 0.01	0.89 ± 0.01	0.85 ± 0.01	−0.07 (−0.09, −0.04)	−0.04 (−0.07, −0.02)
	Adjusted	0.89 ± 0.01	0.91 ± 0.01	0.89 ± 0.01	−0.003 (−0.04, 0.03)	−0.02 (−0.04, 0.01)
WOMAC						
Pain	Crude	0.96 ± 0.11	1.45 ± 0.10	2.62 ± 0.15	1.65 (1.23, 2.08)	1.16 (0.74, 1.59)
	Adjusted	1.45 ± 0.11	1.19 ± 0.11	1.99 ± 0.15	0.53 (0.07, 1.00)	0.80 (0.38, 1.21)
Stiffness	Crude	0.55 ± 0.06	0.79 ± 0.06	1.14 ± 0.08	0.59 (0.37, 0.81)	0.35 (0.12, 0.57)
	Adjusted	0.75 ± 0.06	0.68 ± 0.06	0.85 ± 0.08	0.10 (−0.15, 0.34)	0.16 (0.06, 0.39)
Function	Crude	2.41 ± 0.34	4.54 ± 0.35	8.32 ± 0.47	5.91 (4.54, 7.28)	3.78 (2.40, 5.16)
	Adjusted	4.37 ± 0.35	3.62 ± 0.33	5.79 ± 0.47	1.42 (−0.04, 2.88)	2.17 (0.85, 3.50)

Values are mean ± SE. SF-8, Medical Outcomes Study Short Form-8.
Adjusted differences in means were calculated by Tukey HSD test after adjustment for age, BMI and grip strength.