Introduction

Musculoskeletal diseases, including osteoarthritis (OA) and osteoporosis (OP), are major public health problems among the elderly that affect activities of daily living (ADL) and quality of life (QOL), leading to increased morbidity and mortality. According to the recent National Livelihood Survey by the Ministry of Health, Labour, and Welfare in Japan, OA is ranked fourth, while falls and osteoporotic fractures are ranked fifth among diseases that cause disabilities and subsequently require support for ADL [1]. Previous studies have reported increased mortality following osteoporotic fractures at the hip and other sites [2], and have estimated that a total of 47,000,000 people (21,000,000 men and 26,000,000 women) aged ≥40 years will eventually be affected by either OA or OP. Considering that the population of Japan is aging very rapidly—more than 22% of the population is aged ≥65 years [3]—a comprehensive and evidence-based prevention strategy for musculoskeletal diseases is urgently needed.

The Japanese Orthopaedic Association has proposed the term 'locomotive syndrome' to designate a condition in high-risk groups with musculoskeletal diseases who are highly likely to require nursing care [4]. Locomotive syndrome is caused by weakening of musculoskeletal organs such as bone, joint, and muscle, which in turn interferes with physical performance, especially self-transportation. Loss of locomotor abilities such as walking causes disabilities requiring support. Therefore, to prevent decline into disability, it is important to maintain a healthy range of bone, joint, muscle, and physical performance.

These four components, bone, joint, muscle, and physical performance, each have objective measurements that can be used as indices to evaluate their present condition. For example, bone mineral density (BMD) is a representative index of the condition of the bone. Joint space width (JSW), joint space area (JSA), and osteophyte area (OPA) are indices reflecting the condition of the joint. Regarding muscle, although the best index remains controversial, hand grip strength can be used to reflect muscle strength [5], and muscle mass is one index of muscle volume [6]. In addition, as objective indices of physical performance, walking speed and/or one-leg standing times are candidates [7, 8]. However, at present, it is difficult to use such indices for evaluating, diagnosing, or predicting the future occurrence and progression of locomotive syndrome in Japan, because there is little information on reference values for such indices to distinguish patients at risk from normal individuals in a large population-based cohort.

In 2005–2007, we began a large-scale population-based cohort study entitled Research on Osteoarthritis/Osteoporosis Against Disability (ROAD), consisting of 3,040 participants in three communities located in urban, mountainous, and coastal areas (baseline study). Following the baseline study, a second survey was performed in the same communities in 2008–2010, in which 2,674 inhabitants participated (second visit).

Through analysis of the baseline data of the ROAD, the age-gender distribution of BMD has been reported as an index for bone mass [3], and the medial and lateral JSW, medial and lateral JSA, OPA, and femorotibial angle of the knee have been reported as indices of the health of joints [9] in these populations. However, there is still scant information regarding the condition of the muscles and physical performance. Therefore, in the present study, we aimed to establish reference values for hand grip strength as an index of muscle power, muscle mass as an index of muscle volume, and walking time and one-leg standing time as indices of physical performance, classified by age and gender, using the data from the second visit of the ROAD study. This information is expected to be valuable for early diagnosis and prevention of locomotive syndrome. In addition, we evaluated the prevalence of disabilities in participants in the ROAD study second visit, and identified associations between hand grip strength, muscle mass, walking time, and one-leg standing time and the presence of disability.

Participants and methods

Participants

Reference values were obtained from the results of cross-sectional measurements of participants enrolled in the second visit of the ROAD study. The ROAD study, which began in 2005, is a nationwide prospective study comprising population-based cohorts established in three communities, such as urban, mountainous, and coastal regions in Japan. Recruitment methods for this study have been described in detail elsewhere [3]. To date, participants in the urban region, aged ≥60 years, were recruited from among those enrolled in a randomly selected cohort study from the previously established Itabashi Ward resident's registration database. The response rate was 75.6%. Participants in the mountainous and coastal regions, aged ≥40 years, were recruited from listings of resident registration. Residents aged ≤60 years in the urban area and ≤40 years in the mountainous and coastal areas who were interested in participating in the study were invited. We have completed development of a baseline database including clinical and genetic information for 3,040 inhabitants aged 23–95 years (1,061 men, 1,979 women).

The second visit of the ROAD study began in 2008 and was completed in 2010. All the participants in the baseline study were invited to participate in the second visit. In addition to the former participants, inhabitants aged ≥60 years in the urban area and those aged ≥40 years in the mountainous and coastal areas who were willing to participate in the ROAD survey performed in 2008–2010 were also included in the second visit. In addition, residents aged ≤60 years in the urban area and ≤40 years in the mountainous and coastal areas who were interested in participating in the study were invited to be examined as well as the baseline.

The inclusion criteria of participants were as follows: (1) ability to walk to the clinic where the survey was performed, (2) ability to provide self-reported data, and (3) ability to understand and sign an informed consent form. No other exclusion criteria were used.

Thus, a total of 2,674 residents (892 men, 1,782 women) aged 21–97 years participated in the second visit. In the present study, we analysed the data for 2,468 individuals (826 men, 1,642 women; mean age 71.8 years); this population comprised 956 individuals (318 men, 638 women) in the urban region, 726 individuals (258 men, 468 women) in the mountainous region, and 786 individuals (250 men, 536 women) in the coastal region who participated in the second visit and were ≥40 years old.

All the participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the participating institutions.

Hand grip strength, muscle mass, walking time, and one-leg standing time

Hand grip strength was measured bilaterally using a Toei Light handgrip dynamometer (Toei Light Co., Ltd., Saitama, Japan). Both hands were tested, and the better value was used to characterise the maximum muscle strength of the subject.

Among the 2,468 participants who participated in the second visit of the ROAD study, 778 residents (248 men, 530 women) in the coastal town of Taiji were examined to determine their segmental muscle mass using the bioelectrical impedance method (BIP; Physion MD; Physion Inc., Kyoto, Japan). We obtained values for the muscle masses of the right and left forearms, upper arms, upper limbs, quadriceps, thighs, lower legs, and lower limbs. This method had previously been validated as having a close correlation to muscle volume as measured by magnetic resonance imaging [10].

Among the 2,468 participants who participated in the second visit of the ROAD study, 1,637 residents (559 men, 1,078 women) of the mountainous town of Hidakagawa and the coastal town of Taiji were examined to determine their walking time. Walking time was measured as the time required to complete a 6-m course. All participants walked the 6-m course twice; they first walked at their usual walking speed and then repeated the course at their fastest pace.

Among the 2,468 participants who participated in the second visit of the ROAD study, one-leg standing time with eyes open was measured on both sides for 2,433 individuals (816 men, 1,617 women). The time until the raised leg was set down on the floor was measured, with a maximum time of 60 s recorded for those who could stand on one leg for at least that length of time. The shorter value of the two measurements was used as the worse side and the longer measurement as the better side for the one-leg standing time of the subject.

Mean values and standard deviations (SDs) of hand grip strength, muscle mass, and walking time were classified by gender and age group (40, 50, 60, 70, and ≥80 s) to establish age-gender reference values for the general population. However, reference values classified by gender and age group for one-leg standing time were established using median (50th percentile) values and 25th–75th percentile ranges. These values were recorded using a maximum time of 60 s for anyone who could exceed that time; thus, the data do not fit a normal distribution, and use of means and SDs is unsuitable for one-leg standing time reference values.

Presence of disability

Disability in the present study was defined as 'cases requiring long-term care' as determined by the long-term care insurance system based on the Long-Term Care Insurance Act of 1997 in Japan. The procedure for identifying cases requiring long-term care is as follows: (1) each municipality establishes a long-term care approval board consisting of clinical experts, physicians, and specialists at the Division of Health and Welfare in each municipal office; (2) the long-term care approval board investigates the insured person using an interviewer-administered questionnaire consisting of 82 items regarding mental and physical condition and makes a screening judgement based on the opinion of a regular doctor; and (3) 'cases requiring long-term care' are determined according to standards for long-term care certification uniformly and objectively applied nationwide [11].

During the 3 years between the baseline and the second visit of the ROAD study, we annually obtained information on the participating residents regarding deaths, changes of residence, and presence or absence of certified disability according to the long-term care insurance system from the public health centres of the participating municipalities.

Statistical analysis

All statistical analyses were performed using Stata statistical software (Stata, College Station, TX, USA). Differences in the values of the indices were tested for significance using analysis of variance for comparisons among multiple groups. Scheffé's least significant difference test was then used for pairs of age groups.

To ascertain associations between the presence of disability and hand grip strength, muscle mass, walking time, and one-leg standing time, logistic regression analyses were performed using the presence of disability (yes, 1; no, 0) as an objective factor, and values for hand grip strength, muscle mass, walking time, and one-leg standing time as the explanatory factor after adjusting for age, gender, and body mass index (BMI, kg/m^2).

Results

Characteristics of participants

Summary characteristics including age, height, weight, and BMI of the participants in the present study are shown in Table 1. Two-thirds of the 2,468 subjects were women, and the mean age of the female participants was 1 year younger than that of the male participants. Height and weight were significantly lower for women than for men, but no significant difference in BMI was noted between the genders. All anthropometric measurements other than BMI of females tended to decrease with age. BMI of women in their 80s and older was significantly lower than that in younger age groups, while there were no significant differences among age groups 40–70 years old.

Reference values for hand grip strength, muscle mass, walking time, and one-leg standing time

Table 1 also shows the age-gender distribution of hand grip strength for both the better and worse sides. Mean hand grip strength in men was significantly higher than that in women ($p < 0.001$) and decreased with age in both men and women ($p < 0.001$).

Mean muscle mass for both forearms, both upper arms, both upper limbs, both quadriceps, both thighs, both lower legs, and both lower limbs are shown in Table 2. Muscle masses for all parts of the body were significantly higher in men than in women ($p < 0.001$). Mean muscle mass in men decreased with age for all areas except the lower leg. Particularly in the quadriceps and thighs, muscle masses in men aged ≥70 were significantly lower than those in their 40s–50s ($p < 0.05$). By contrast, although muscle mass for women aged ≥80 and older tended to be lower than those of younger age groups (other than the lower legs), there

Table 1 Mean values (standard deviation) of anthropometric measurements and hand grip strength of the participants classified by sex and gender

Age strata (years)	Number of subjects	Weight (kg)	Height (cm)	Body mass index (g/cm^2)	Grip strength (better side) (kg)	Grip strength (worse side) (kg)
Men						
40–49	32	73.5 (10.2)	170.3 (7.3)	25.4 (3.6)	49.5 (8.2)	49.3 (8.4)
50–59	100	68.8 (10.6)	168.0 (5.2)	24.3 (3.3)	47.3 (7.0)	42.6 (6.9)
60–69	137	65.4 (11.1)[a]	165.2 (6.2)[a,b]	23.9 (3.5)	41.4 (6.6)[a,b]	36.9 (7.9)[a,b]
70–79	308	60.0 (8.1)[a,b,c]	161.1 (5.7)[a,b,c]	23.1 (2.7)[a,b]	35.4 (6.8)[a,b,c]	31.5 (7.1)[a,b,c]
80 and older	249	57.2 (8.9)[a,b,c,d]	159.7 (6.0)[a,b,c]	22.4 (2.9)[a,b,c]	29.7 (6.2)[a,b,c,d]	26.3 (6.3)[a,b,c,d]
Total	826	61.6 (10.3)	162.5 (6.7)	23.3 (3.1)	36.6 (9.1)	32.7 (9.1)
Women						
40–49	93	55.9 (9.5)	157.0 (4.4)	22.6 (3.5)	31.2 (4.3)	28.2 (4.4)
50–59	191	55.3 (8.9)	154.4 (5.8)[a]	23.2 (3.7)	28.7 (4.9)[a]	25.4 (4.9)[a]
60–69	316	54.2 (8.0)	152.0 (5.5)[a,b]	23.4 (3.2)	26.6 (4.3)[a,b]	23.77 (4.5)[a,b]
70–79	599	51.3 (8.5)[a,b,c]	148.4 (5.9)[a,b,c]	23.3 (3.5)	22.6 (4.6)[a,b,c]	19.7 (4.7)[a,b,c]
80 and older	443	47.4 (8.3)[a,b,c,d]	145.5 (5.9)[a,b,c,d]	22.4 (3.6)[c,d]	19.4 (4.4)[a,b,c,d]	16.6 (4.6)[a,b,c,d]
Total	1,642	51.6 (8.9)	149.5 (6.7)	23.0 (3.5)	23.7 (5.8)	20.8 (5.8)

[a] Significantly different ($p < 0.05$) from values of the age group in their 40s

[b] Significantly different ($p < 0.05$) from values of the age group in their 50s

[c] Significantly different ($p < 0.05$) from values of the age group in their 60s

[d] Significantly different ($p < 0.05$) from values of the age group in their 70s

Table 2 Mean values (standard deviation) of segmental muscle mass (kg) in total right and left sides classified by age and gender

Age strata (years)	Number of subjects	Forearm	Upper arm	Upper limb	Quadriceps	Thigh	Lower leg	Lower limb
Men								
40–49	25	1.20 (0.19)	1.59 (0.36)	2.79 (0.54)	3.91 (0.64)	7.76 (1.19)	3.41 (0.66)	11.16 (1.69)
50–59	60	1.18 (0.16)	1.53 (0.28)	2.71 (0.41)	3.73 (0.64)	7.45 (1.22)	3.41 (0.66)	10.86 (1.60)
60–69	67	1.15 (0.17)	1.50 (0.28)	2.65 (0.42)	3.50 (0.68)	7.02 (1.28)	3.52 (0.86)	10.54 (1.89)
70–79	66	1.17 (0.20)	1.43 (0.28)	2.60 (0.46)	3.37 (0.66)[a]	6.78 (1.26)[a]	3.51 (0.68)	10.29 (1.70)
80 and older	30	1.11 (0.17)	1.37 (0.26)	2.48 (0.38)	3.10 (0.62)[a,b]	6.27 (1.18)[a,b]	3.92 (1.11)	10.18 (2.05)
Total	248	1.16 (0.18)	1.48 (0.29)	2.65 (0.44)	3.52 (0.69)	7.04 (1.30)	3.53 (0.80)	10.57 (1.79)
Women								
40–49	67	0.77 (0.12)	0.86 (0.19)	1.63 (0.30)	2.65 (0.60)	5.37 (1.12)	2.65 (0.47)	8.02 (1.45)
50–59	124	0.76 (0.10)	0.82 (0.16)	1.58 (0.24)	2.56 (0.44)	5.20 (0.82)	2.58 (0.51)	7.78 (1.20)
60–69	161	0.78 (0.11)	0.84 (0.16)	1.62 (0.25)	2.55 (0.45)	5.18 (0.84)	2.57 (0.42)	7.74 (1.10)
70–79	130	0.80 (0.12)[b]	0.85 (0.16)	1.66 (0.27)	2.54 (0.46)	5.17 (0.85)	2.66 (0.53)	7.83 (1.24)
80 and older	48	0.79 (0.43)	0.82 (0.16)	1.61 (0.28)	2.39 (0.45)	4.90 (0.84)	2.91 (0.69)[b,c]	7.81 (1.38)
Total	530	0.78 (0.11)	0.84 (0.16)	1.62 (0.26)	2.55 (0.47)	5.18 (0.88)	2.63 (0.51)	7.81 (1.23)

[a] Significantly different ($p < 0.05$) from values of the age group in their 40s

[b] Significantly different ($p < 0.05$) from values of the age group in their 50s

[c] Significantly different ($p < 0.05$) from values of the age group in their 60s

were no specific trends in muscle mass among age groups ≤79 years old. However, as for men, the muscle mass of the quadriceps in women tended to decline with age, although the difference was not statistically significant.

Mean 6-m walking time and the calculated walking speed (m/s) using the walking time, classified by age and gender, are shown in Table 3. Six-meter walking time was significantly lower in men than in women ($p < 0.05$), indicating that men tended to walk faster than women in this study population. Mean 6-m walking time for both men and women increased with age. In particular, 6-m walking times for men and women ≥70 years old were significantly higher than those in younger age groups ($p < 0.05$).

Table 4 shows median one-leg standing time classified by age and gender with 25th–75th percentile ranges. For both men and women in their 40s–50s, all median, 25th percentile, and 75th percentile values were 60 s, with no gender difference. One-leg standing times for men ≥60 years old tended to be higher than those for women, and median values declined with age in both men and women.

Prevalence of disability among subjects ≥65 years old

Among the 2,468 participants in the second visit of the ROAD study, we surveyed 1,845 subjects (625 men, 1,220 women) ≥65 years old and obtained information on the presence or absence of disability certified for long-term care insurance. We found a total of 149 individuals (8.1%; 36 men, 5.8%; 113 women, 9.3%) that were certified as requiring support. Figure 1 shows the prevalence of disability classified by gender and age. The prevalence of disability in men 65–69, 70–74, 75–79, and ≥80 years old was 0.0, 1.0, 6.3, and 8.8%, respectively, and that in women in the same age groups was 3.4, 3.5, 9.2, and 14.7%, respectively (Fig. 1). The prevalence of disability in women was significantly higher than that in men ($p < 0.05$) and increased with age in both genders ($p < 0.01$).

Associations between disability and hand grip strength, muscle mass, walking speed, and one-leg standing time

Logistic regression analysis was performed using the presence of disability (1, yes; 0, no) as an objective factor, and hand grip strength on the better side and the worse side; muscle mass of the forearms, upper arms, upper limbs, quadriceps, thighs, lower legs, and lower limbs; walking time for 6 m at the usual pace and at the fastest pace; and quartile of one-leg standing time [0: 0–25% (highest quartile), 1: 25–50% (higher quartile), 2: 50–75% (lower quartile), 3: 75–100% (the lowest quartile] on the better and worse sides as explanatory factors, after adjusting for age, gender, and BMI. No significant associations were found between the presence of disability and hand grip strength, muscle mass, or one-leg standing time. However, there were significant associations between the presence of disability and 6-m walking time at the usual

Table 3 Mean values (standard deviation) of 6-m walking time (s) and walking speed (m/s) with usual pace and the fastest pace classified by age and gender

Age strata (years)	Number of subjects	Usual pace		Fastest pace	
		Time for 6 m (s)	Walking speed (m/s)	Time for 6 m (s)	Walking speed (m/s)
Men					
40–49	32	4.4 (0.6)	1.38 (0.19)	3.0 (0.5)	2.09 (0.43)
50–59	100	4.8 (0.9)	1.29 (0.20)	3.2 (0.6)	1.97 (0.36)
60–69	134	5.1 (0.9)	1.21 (0.20)[a]	3.4 (0.7)	1.82 (0.33)[a]
70–79	196	5.9 (1.8)[a,b,c]	1.09 (0.25)[a,b,c]	4.0 (1.4)[a,b,c]	1.62 (0.39)[a,b,c]
80 and older	97	6.8 (3.0)[a,b,c,d]	0.99 (0.33)[a,b,c,d]	4.5 (1.8)[a,b,c,d]	1.48 (0.44)[a,b,c]
Total	559	5.6 (1.9)	1.15 (0.27)	3.7 (1.3)	1.73 (0.42)
Women					
40–49	92	4.7 (1.0)	1.32 (0.24)	3.2 (0.6)	1.95 (0.31)
50–59	190	4.9 (0.9)	1.27 (0.23)	3.3 (0.7)	1.87 (0.33)
60–69	299	5.1 (1.1)	1.22 (0.23)	3.7 (0.8)	1.71 (0.32)[a,b]
70–79	345	6.3 (2.4)[a,b,c]	1.03 (0.25)[a,b,c]	4.4 (1.5)[a,b,c]	1.46 (0.36)[a,b,c]
80 and older	152	8.4 (3.9)[a,b,c,d]	0.82 (0.27)[a,b,c,d]	5.8 (2.7)[a,b,c,d]	1.17 (0.36)[a,b,c,d]
Total	1,078	5.9 (2.4)	1.12 (0.29)	4.1 (1.6)	1.60 (0.42)

[a] Significantly different ($p < 0.05$) from values of the age group in their 40s

[b] Significantly different ($p < 0.05$) from values of the age group in their 50s

[c] Significantly different ($p < 0.05$) from values of the age group in their 60s

[d] Significantly different ($p < 0.05$) from values of the age group in their 70s

Table 4 Values of median (25–75 percentile) of one-leg standing time (s, maximum = 60 s) in a better side and a worse side classified by age and gender

Age strata (years)	Number of subjects	One-leg standing time (better side) (s)	One-leg standing time (worse side) (s)
Men			
40–49	32	60 (60–60)	60 (60–60)
50–59	99	60 (60–60)	60 (60–60)
60–69	136	60 (34.5–60)	45 (14.25–60)
70–79	303	27 (9–60)	9 (4–35)
80 and older	246	8 (4–32)	4 (2–12)
Total	816	39.5 (8–30)	14 (4–60)
Women			
40–49	92	60 (60–60)	60 (60–60)
50–59	191	60 (60–60)	60 (43–60)
60–69	317	60 (41.5–60)	43 (13–60)
70–79	593	21 (8–57.5)	8 (3–25)
80 and older	424	7 (3–18.8)	3 (2–7)
Total	1,617	31 (8–60)	12 (4–60)

pace [+1 s, odds ratio (OR) 1.15, 95% confidential interval (CI) 1.07–1.24, $p < 0.001$] and at the fastest pace (+1 s, OR 1.22, 95% CI 1.08–1.38, $p < 0.01$). In addition, there were significant associations between the presence of disability and walking speed at the usual pace (+1 m/s, OR 0.07, 95% CI 0.02–0.27, $p < 0.001$) and at the fastest pace (+1 m/s, OR 0.16, 95% CI 0.06–0.41, $p < 0.001$).

Discussion

In this study, we established age-gender-classified mean values for hand grip strength as an index of muscle strength, muscle mass as an index of muscle volume, and walking time and median one-leg standing time as indices of physical performance, using data for a large-scale

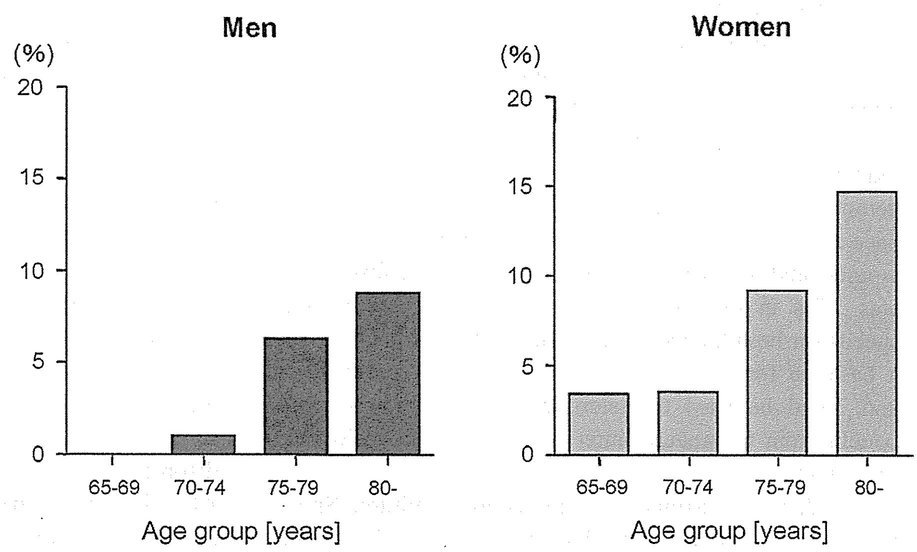

Fig. 1 Prevalence of disability among subjects ≥65 years old classified by gender and age

population-based cohort. We found that mean hand grip strength, muscle mass, walking time, and median one-leg standing time were higher in men than in women, and decreased with age (with the exception of the muscle mass of the lower legs).

The Japanese Ministry of Education, Culture, Sports, Science, and Technology has reported ranges for physical strength and sporting ability in 69,745 Japanese men and women 6–79 years old. Mean hand grip strength in both men and women reaches peak values between the ages of 20–40, and decreases with age after 40 [12]. In the present study of a population aged ≥40 years, hand grip strength declined significantly with age, consistent with the previous report of the Japanese government.

Although computed tomography or MRI scans are the most reliable methods of measuring segmental muscle mass, these methods are not suitable for a large-scale population-based study. The BIA method is rapid, inexpensive, portable, and importantly, a noninvasive measuring method. Previous studies have shown that there is a strong correlation between BIA resistance and measurements of skeletal muscle mass in the arms [13], legs [13], and whole body [14]. For the BIA method used in the present study, Miyatani et al. [10] had previously compared values for muscle mass using a series of cross-sectional images of the forearm, upper arm, lower leg, and thigh on the right side of 22 male subjects as determined by the BIA and MRI methods. The BIA impedance index (L^2/Z) for every segment, calculated as the ratio of the segment length squared to the impedance, was significantly correlated with the muscle volume measured by MRI, with $r = 0.902$–0.976 ($p < 0.05$). These previous results demonstrate that the BIA method used in the present study is sufficiently reliable as an index of muscle volume.

In the present study, age-related differences were observed in the thighs and quadriceps. In addition, the age-related decreases in muscle mass were greater in the lower limbs than in the upper limbs, and in proximal sites than in distal sites. Yamada et al. [15] estimated the bioelectrical impedance (BI) index, calculated as the ratio of the square of segmental length to impedance in a Japanese population consisting of 1,006 individuals (374 men, 632 women) and reported that the BI index decreased most with age in the thighs, whereas there were no significant age-related changes in the forearms or lower limbs. Miyatani et al. [16] studied muscle thickness at nine sites, the forearm, anterior and posterior upper arm, abdomen, subscapular, anterior and posterior thigh, and anterior and posterior lower leg, using brightness-mode ultrasonography in 348 Japanese men aged 20–79 years. They found a greater decrease in muscle thickness in the trunk and anterior thigh than at other sites, consistent with our results. They speculated that site-related differences in muscle loss with aging may be attributed to age-related changes in the patterns of loading to and/or activation of individual muscles in daily life. However, because these results were obtained from a cross-sectional study, longitudinal data would be required to determine the mechanism of these differences. We have begun the third visit of the ROAD study, 6 years after the baseline and 3 years after the second visit, to measure losses of skeletal muscle mass at various sites. Losses of muscle mass in the quadriceps and/or thighs may result in a decrease in walking ability, including walking speed. Therefore, establishment of reference values for muscle mass is useful for prediction of future disability.

Walking ability is regarded as the most important activity for the elderly to maintain an independent life in the community, and walking speed is an important index of walking ability. Reference values have been published for populations in western countries [17, 18]; however, there has been little information available for the Japanese population. Takahashi et al. [19] surveyed walking speed at 130 crosswalks and reported that at least 1.0 m/s was required to safely cross the street. In the present study, we determined that the mean 6-m walking time at the usual pace at an age of $\geq$40 years was 5.6 s for men and 5.9 s for women, and the mean 6-m walking time at the fastest pace was 3.7 s in men and 4.1 s in women. These walking speeds for both the usual pace and the fastest pace provide a baseline for clinical judgments of patient performance and could be used to determine which subjects would benefit from therapeutic intervention to improve locomotive function.

The Japanese Ministry of Education, Culture, Sports, Science and Technology published mean values for one-leg standing time with a maximum time of 120 s using 5,500 individuals (2,741 men, 2,759 women) with an age range of 65–79 years in each prefecture who participated in an examination of sporting ability, including walking ability [12]. They reported that mean one-leg standing times for men 65–69, 70–74, and 75–79 years old were 79.9, 66.5, and 50.5 s, respectively, and those for women were 80.8, 62.1, and 45.0 s, respectively. These values were measured up to 120 s, and ours were measured up to 60 s. Because the measuring method was different and their outcomes are means while our results are medians, the results cannot be compared directly. However, one-leg standing time was significantly lower with age in both studies. Again, establishment of reference values for physical performance, including walking and standing ability, would be useful for prediction of future disability.

We then evaluated associations between hand grip strength, muscle mass, walking time, and one-leg standing time, as indices reflecting components of locomotive syndrome and the presence of disability. We found that the 6-m walking time may be a useful index for detection of disability. To evaluate the independence of elderly persons in daily life, physical performance has been measured using various outcomes. Walking speed has been reported to be one important index that can predict future disability, hospitalisation, and mortality in the general geriatric population [20, 21]. In a Japanese population, Shinkai et al. [22] demonstrated that lower scores on baseline performance measures, particularly maximum walking speed, predicted an increased risk of onset of functional dependence, based on their 6-year follow-up of a cohort in a rural community consisting of 736 participants. In the present study, a 1-s slower normal walking time for 6 m was associated with a 15% increase in the presence of disability, and a 1-s slower fastest walking time for 6-m was associated with a 22% increase in the presence of disability. Our study evaluated only walking ability and the presence of disability, not the occurrence of disability; however, we expect to follow these populations and clarify the predictive ability of walking speed for the occurrence of disability over the next few years.

On the other hand, no associations were found between indices such as hand grip strength, muscle mass, and one-leg standing time and the presence of disability. There is growing evidence that reduced hand grip strength is associated with adverse outcomes in older years, including morbidity, lower quality of life, higher fracture rates, increased length of hospital stay, and mortality [23–25]. Progressive decline in muscle mass has been defined as sarcopenia, which represents an impaired state of health associated with morbidity disorders, increased risk of falls and fractures, impaired ADL, loss of independence, and increased risk of death [6, 26–29]. Lang et al. [29] stated that loss of muscle mass and power increases the difficulties associated with procuring adequate nutrition and the effort required to undertake exercise; the combination of nutritional loss and reduced physical activity levels results in further loss of muscle mass and power. The resulting decrements in power, endurance, and physical performance lead to a loss of independence. In addition to muscle strength and mass, balance appears to be an important index of disability. Shinkai et al. [22] measured the one-leg standing time of 736 participants in a cohort established in a rural community, and the individuals in the lowest performance quartile had a significantly higher occurrence of disability.

Self-selection bias is suggested as a possible reason for the lack of associations between hand grip strength, muscle mass, and one-leg standing time and disability observed here, compared with previous reports. Self-selection bias is one type of sampling bias exhibited by subjects who voluntarily enrol in an epidemiological study. In this second visit of the ROAD study, volunteers who could walk to the clinic where the survey was performed, and could understand and sign an informed consent form, and who wanted to learn about their bone and joint conditions were welcomed. Therefore, the participants in the second survey may have been healthier than the general Japanese population. In fact, the estimated number of persons with disability in Japan using the age-gender prevalence of the second visit and the age-gender distribution of the Japanese population based on the national census in 2007 would be estimated at 1,510,000 (350,000 men, 1,160,000 women), considerably lower than the 4,940,000 reported by the government in 2010. Thus, self-selection bias likely affected the reference values; the reference values for hand grip strength, muscle mass, and one-leg standing time obtained from the present study may be higher, and walking speed faster, than the actual values. However, self-selection bias is somewhat unavoidable in such an examination, because it is impossible to obtain measurements for individuals who cannot grasp a handgrip dynamometer or walk 6 m. This bias should be taken into consideration when reference values are used, including not only those obtained from the present study, but also from the national survey of physical strength and sporting ability published by the government.

In addition to self-selection bias, this study has several limitations. First, our results were obtained from a cross-sectional study of the second visit of the ROAD study; thus, we can not conclude causal relationships between such indices and disability, since some of the indices, such as muscle mass and one-leg standing time, were first introduced and performed during the second visit. We have begun the third visit of the ROAD study to clarify the relationships between physical performance and the occurrence of disability. Once the significance of indices reflecting components of locomotive syndrome can be determined as predictors for the occurrence of disability, appropriate thresholds can be developed as predictors of future disability. In addition, because of the lack of sufficient information, we could not determine the disorders that caused the disability. Thus, the disabled status of the participants in the present study might have been affected by various diseases such as cardiovascular diseases, dementia, or other diseases. However, regardless of the cause of disability, we found that walking ability was significantly associated with the presence of disability.

Conclusions

We have established reference values for hand grip strength, muscle mass, walking time, and one-leg standing time using data for a large-scale population-based cohort, and identified gender and age differences in the reference values. In addition, we determined that walking ability, including walking time and walking speed at the usual and maximum pace, was significantly associated with the presence of disability.

Acknowledgments This work was supported by Grants-in-Aid for Scientific Research B20390182 (Noriko Yoshimura), C20591737 (Toru Akune), and C20591774 (Shigeyuki Muraki); for 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; it was also supported by grants H17-Men-eki-009 (Director, Kozo Nakamura), H18-Choujyu-037 (Director, Toshitaka Nakamura), and H20-Choujyu-009 (Director, Noriko Yoshimura), H23-Choujyu-002 (Director, Toru Akune) from the Ministry of Health, Labour, and Welfare of Japan. Further, this study was 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, 2010-2, Director, Hiroshi Kawaguchi). The authors wish to thank Mrs. Tomoko Takijiri, Mrs. Kumiko Shinou, Mrs. Rie Takiguchi, Mrs. Kyoko Maeda, Ms. Ikuyo Ueyama, Mrs. Michiko Mori, Mrs. Hisayo Sugimoto, and other members of the public office in Hidakagawa Town; and Mrs. Tamako Tsutsumi, Mrs. Kanami Maeda, Mr. Shoichi Shimoichi, Mrs. Megumi Takino, Mrs. Shuko Okada, Mrs. Kazuyo Setoh, Mrs. Chise Ryouno, Mrs. Miki Shimosaki, Mrs. Chika Yamaguchi, Mrs. Yuki Shimoji, and other members of the public office in Taiji Town for their assistance in locating and scheduling participants for examination. We also thank Ms. Kyoko Yoshimura, Mrs. Toki Sakurai, and Mrs. Saeko Sahara for their assistance in data reduction and administration.

Conflict of interest No conflict of interest has been declared by the authors.

References

1. Ministry of Health, Labour and Welfare. The outline of the results of National Livelihood Survey 2007. Available at http://www.mhlw.go.jp/toukei/list/20-19-1.html.
2. Muraki S, Yamamoto S, Ishibashi H, Nakamura K. Factors associated with mortality following hip fracture in Japan. J Bone Miner Metab. 2006;24:100–4.
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. 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. 2009;27:620–8.
4. Nakamura K. Locomotive syndrome in an aging society. J Jpn Orthop Assoc. 2008;82:1–2. in Japanese.
5. Ministry of Internal Affairs and Communications. Vital statistics in Japan: The number of inhabitants and households based on resident registration in Japan 2010. Available at http://www.soumu.go.jp/menu_news/s-news/01gyosei02_01000001.html (in Japanese).
6. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinková E, Vandewoude M, Zamboni M. European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39:412–23.
7. Ostir GV, Kuo YF, Berges IM, Markides KS, Ottenbacher KJ. Measures of lower body function and risk of mortality over 7 years of follow-up. Am J Epidemiol. 2007;166:599–605.
8. Michikawa T, Nishiwaki Y, Takebayashi T, Toyama Y. One-leg standing test for elderly populations. J Orthop Sci. 2009;14:675–85.
9. Oka H, Muraki S, Akune T, Nakamura K, Kawaguchi H, Yoshimura N. Normal and threshold values of radiographic parameters for knee osteoarthritis using a computer-assisted measuring system (KOACAD): The ROAD Study. J Orthop Sci. 2010;15:784–9.
10. Miyatani M, Kanehisa H, Masuo Y, Ito M, Fukunaga T. Validity of estimating limb muscle volume by bioelectrical impedance. J Appl Physiol. 2001;91:386–94.
11. Ministry of Health, Labour and Welfare. Long-term care insurance in Japan. Available at http://www.mhlw.go.jp/english/topics/elderly/care/index.html.
12. Ministry of Education, Culture, Sports, Science and Technology. The outline of the results of physical strength and sporting ability 2008. Available at http://www.mext.go.jp/b_menu/toukei/001/1285611.htm (in Japanese).

13. Petrobelli A, Morini P, Battistini N, Chiumello G, Nuñez C, Heymsfield SB. Appendicular skeletal muscle mass: prediction from multiple frequency segmental bioimpedance analysis. Eur J Clin Nutr. 1998;52:507–11.
14. Janssen I, Heymsfield SB, Baumgartner RN, Ross R. Estimation of skeletal muscle mass by bioelectrical impedance analysis. J Appl Physiol. 2000;89:465–71.
15. Yamada Y, Kimura M, Nakamura E, Masuo Y, Oda S. Limb muscle mass decrease with aging in Japanese men and women aged 15–97 yr. Jpn J Phys Fitness Sports Med. 2007;56:461–72. (in Japanese).
16. Miyatani M, Kanehisa H, Azuma K, Kuno S, Fukunaga T. Site-related differences in muscle loss with aging: a cross-sectional survey on the muscle thickness in Japanese men aged 20 to 79 years. Int J Sport Health Sci. 2003;1:34–40.
17. Hinmann JE, Cunningham DA, Rechnitzcr PA, Paterson DH. Age related changes in speed of walking. Med Sci Sports Exerc. 1988;20:161–6.
18. Bohannon RW. Comfortable and maximum walking speed of adults aged 20–79 years: reference values and determinants. Age Ageing. 1997;26:15–9.
19. Takahashi S, Toriida M, Tayama H. A study on the standard of gait evaluation—by an actual investigation of crosswalks. Rigaku Ryoho Gaku. 1989;16:261–6. in Japanese.
20. Cesari M, Kritchevsky SB, Penninx BW, Nicklas BJ, Simonsick EM, Newman AB, Tylavsky FA, Brach JS, Satterfield S, Bauer DC, Visser M, Rubin SM, Harris TB, Pahor M. Prognostic value of usual gait speed in well-functioning older people—results from the Health, Aging and Body Composition Study. J Am Geriatr Soc. 2005;53:1675–80.
21. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med. 1995;332: 556–61.
22. Shinkai S, Watanabe S, Kumagai S, Fujiwara Y, Amano H, Yoshida H, Ishizaki T, Yukawa H, Suzuki T, Shibata H. Walking speed as a good predictor for the onset of functional dependence in a Japanese rural community population. Age Ageing. 2000;29: 441–6.
23. Muraki S, Akune T, Oka H, En-yo Y, Yoshida M, Saika A, Suzuki T, Yoshida H, Ishibashi H, Tokimura F, Yamamoto S, Nakamura K, Kawaguchi H, Yoshimura N. Association of radiographic and symptomatic knee osteoarthritis with health-related quality of life in a population-based cohort study in Japan: The ROAD Study. Osteoarthr Cartil. 2010;18:1227–34.
24. Sirola J, Rikkonen T, Tuppurainen M, Jurvelin JS, Kroger H. Association of grip strength change with menopausal bone loss and related fractures: a population based follow-up study. Calcif Tissue Int. 2006;78:218–26.
25. Bohannon RW. Hand-grip dynamometry predicts future outcomes in aging adults. J Geriatr Phys Ther. 2008;31:10–313.
26. Lauretani F, Russo CR, Bandinelli S, Bartali B, Cavazzini C, Di Iorio A, Corsi AM, Rantanen T, Guralnik JM, Ferrucci L. Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. J Appl Physiol. 2003;95:1851–60.
27. Rolland Y, Czerwinski S, Abellan Van Kan G, Morley JE, Cesari M, Onder G, Woo J, Baumgartner R, Pillard F, Boirie Y, Chumlea WM, Vellas B. Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives. J Nutr Health Aging. 2008;12:433–50.
28. Topinková E. Aging, disability and frailty. Ann Nutr Metab. 2008;52(Suppl 1):s6–11.
29. Lang T, Streeper T, Cawthon P, Baldwin K, Taaffe DR, Harris TB. Sarcopenia: etiology, clinical consequences, intervention, and assessment. Osteoporos Int. 2010;21:543–59.

Association of Knee Osteoarthritis with the Accumulation of Metabolic Risk Factors Such as Overweight, Hypertension, Dyslipidemia, and Impaired Glucose Tolerance in Japanese Men and Women: The ROAD Study

NORIKO YOSHIMURA, SHIGEYUKI MURAKI, HIROYUKI OKA, HIROSHI KAWAGUCHI, KOZO NAKAMURA, and TORU AKUNE

ABSTRACT. ***Objective.*** To clarify the association of knee osteoarthritis (KOA) with overweight (OW), hypertension (HTN), dyslipidemia (DL), and impaired glucose tolerance (IGT), which are components of metabolic syndrome (MS), in a Japanese population.

Methods. We enrolled 1690 participants (596 men, 1094 women) from the large-scale cohort study Research on Osteoarthritis Against Disability (ROAD), begun in 2005 to clarify epidemiologic features of OA in Japan. KOA was evaluated by the Kellgren-Lawrence grade, minimum joint space width (MJSW), minimum joint space area (JSA), and osteophyte area (OPA). OW, HTN, DL, and IGT were assessed using standard criteria.

Results. The prevalence of KOA in the total population in the age groups ≤ 39, 40–49, 50–59, 60–69, 70–79, and ≥ 80 years was 2.2%, 10.7%, 28.2%, 50.8%, 69.0%, and 80.5%, respectively. Logistic regression analyses after adjustment for age, sex, regional difference, smoking habit, alcohol consumption, physical activities, regular exercise, and history of knee injuries revealed that the OR of KOA significantly increased according to the number of MS components present (1 component: OR 1.21, 95% CI 0.88–1.68, $p = 0.237$; 2 components: OR 1.89, 95% CI 1.33–2.70, $p < 0.001$; 3 or more components: OR 2.72, 95% CI 1.77–4.18; $p < 0.001$). The number of MS components was inversely related to medial MSJW ($ß = -0.148$, $R^2 = 0.21$, $p < 0.001$), medial JSA (women only; $ß = -0.096$, $R^2 = 0.18$, $p = 0.001$), and positively related to OPA ($ß = 0.12$, $R^2 = 0.11$, $p < 0.001$).

Conclusion. The accumulation of MS components is significantly related to presence of KOA. MS prevention may be useful to reduce cardiovascular disease and KOA risk. (First Release Feb 15 2011; J Rheumatol 2011;38:921–30; doi:10.3899/jrheum.100569)

Key Indexing Terms:
EPIDEMIOLOGY METABOLIC SYNDROME KNEE OSTEOARTHRITIS
RISK FACTORS ROAD STUDY

Osteoarthritis (OA), which causes cartilage and disc degeneration and osteophyte formation at joints in the limbs and spine, is a major public health problem in the elderly that affects activities of daily living (ADL) and quality of life, leading to increased morbidity and mortality[1,2,3]. According to the recent National Livelihood Survey by the Ministry of Health, Labour and Welfare in Japan, OA is ranked fourth among diseases that cause disabilities requiring support and longterm care[4].

In the same report, cardiovascular disease (CVD) is

From the Department of Joint Disease Research, and the Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, Graduate School of Medicine; and the Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan.

Supported by Grants-in-Aid for Scientific Research B20390182 (N. Yoshimura), C20591737 (T. Akune), C20591774 (S. Muraki), and the Young Scientists A18689031 (H. Oka). Collaborating research with NSF 08033011-00262 (Director, N. Yoshimura) from the Ministry of Education, Culture, Sports, Science and Technology, and H17-Men-eki-009 (Director, K. Nakamura), H18-Choujyu-037 (Director, T. Nakamura), and H20-Choujyu-009 (Director, N. Yoshimura) from the Ministry of Health, Labour and Welfare in Japan. This study was also supported by grants from the Japan Osteoporosis Society (N. Yoshimura), Nakatomi Foundation (N. Yoshimura), and research aid from the Japanese Orthopaedic Association (Director, H. Kawaguchi).

N. Yoshimura, MD, PhD, Department of Joint Disease Research, 22nd Century Medical and Research Center, Graduate School of Medicine, The University of Tokyo; S. Muraki, MD, PhD, Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, Graduate School of Medicine, The University of Tokyo; H. Oka, MD, Department of Joint Disease Research, 22nd Century Medical and Research Center, Graduate School of Medicine, The University of Tokyo; H. Kawaguchi, MD, PhD; K. Nakamura, MD, PhD, Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo; T. Akune, MD, PhD, Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, Graduate School of Medicine, The University of Tokyo.

Address correspondence to Dr. N. Yoshimura, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. E-mail: yoshimuran-ort@h.u-tokyo.ac.jp

Accepted for publication December 21, 2010.

ranked first in causing disabilities in the elderly[4]. Most individuals who develop CVD have multiple risk factors[5]. The presence of these risk factors in specific combinations, called metabolic syndrome (MS), is a complex risk factor that predisposes affected individuals to CVD morbidity and mortality. Although various terms have been used to define MS, it is generally thought to consist of a combination of overweight (OW), hypertension (HTN), dyslipidemia (DL), and impaired glucose tolerance (IGT)[6].

Knee OA (KOA) and MS share age and obesity as risk factors[1,7,8,9,10,11]. Many investigators have considered the association of OA with other components of MS. In an early population study, Lawrence first reported that diastolic blood pressure was associated with KOA in women[12]. Regarding DL, Kellgren reported a significant association between women with hand OA and above-average serum cholesterol levels in the 1960s[13]. Cimmino and Cutolo examined the role of glucose and OA, and observed significantly higher levels of plasma glucose in women with OA than in those without OA[14]. Although contradictory findings regarding the association of such metabolic factors with OA have been reported[15,16,17,18,19], Hart, *et al* found that metabolic factors such as blood glucose, hypercholesterolemia, and even treated HTN were associated with the development of KOA. Based on that evidence, they proposed that the etiology of OA had an important systemic and metabolic component[20]. This hypothesis has been supported by data from several population-based studies performed in the United States[21,22]. However, to our knowledge, few population-based studies have demonstrated a dose-response relationship between the severity of KOA and an increasing number of the components of MS. Our first purpose was to clarify the association between the presence of KOA, defined using the Kellgren-Lawrence (KL) scale, and the number of MS components in a Japanese population.

Moreover, in most of these studies that confirmed the association between the presence of KOA and the components of MS, KOA was defined according to KL grade[23]. KL grade is the most conventional system for measuring the radiographic severity of KOA, but does not separately assess joint space narrowing and osteophyte formation. Accumulating evidence has shown that osteophytosis and joint space narrowing have distinct etiologic mechanisms, and their progression is neither constant nor proportional[24,25,26]. Thus, to examine the factors associated with KOA, these 2 OA features should be assessed separately. However, no reports to date have clarified the association of indices of KOA, such as minimum joint space width (MJSW), joint space area (JSA), and osteophyte area (OPA), with the accumulation of the number of components of MS. Our second purpose was to determine whether the accumulation of MS components influenced the values of MJSW, JSA, and OPA.

Further, MS is an emerging epidemic in both men and women worldwide, and with the increase in the global population of Asians, an understanding of the epidemiology of diseases as they relate to Asian populations is required. We have reported that the prevalence of KOA was much higher in a Japanese population than in elderly whites in the United States and Europe, although not largely different from that of African American and Chinese populations[27]. In contrast, the prevalence of MS in East Asian countries including China, Korea, and Japan was reported to be lower than in white populations[28]. In light of the rapid increase in the population of Asian countries, prevention strategies for obesity-related chronic diseases such as MS and KOA should be implemented immediately. Our final aim was to clarify the association between MA components and KOA in people of Asian ethnicity.

MATERIALS AND METHODS

Study population. We used the cohorts established in 2005 for a program called Research on Osteoarthritis Against Disability (ROAD). The ROAD study is a nationwide, prospective study of OA composed of population-based cohorts in several communities in Japan. Details of the cohort profile have been reported[29,30], thus the study population is described here only in brief. We created a baseline database including clinical and genetic information from 3040 residents of Japan (1061 men and 1979 women) with a mean age (SD) of 70.3 (11.0) years [71.0 (10.7) years in men and 69.9 (11.2) years in women]. These subjects were recruited from resident registration listings in 3 communities with different characteristics: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama.

We enrolled 1690 Japanese subjects (596 men; 1094 women) residing in the mountainous and coastal areas. Table 1 lists the background characteristics of all the participants. All participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo. Participants completed an interviewer administered questionnaire of 400 items that included lifestyle information such as occupation, smoking habit, alcohol consumption, family history, medical history, physical activity, reproductive variables, and health-related quality of life. Anthropometric measurements included height, weight, waist length (seaside region only), wrist circumference, bilateral grip strength, and body mass index [BMI; weight (kg)/height $(m)^2$]. Systolic and diastolic blood pressure (BP) were measured by an experienced public health nurse using a mercury sphygmomanometer. Medical information on systemic, local, and mental health status, including information concerning knee, hip, and lower back pain; swelling and range of motion of the joints; and patellar and Achilles tendon reflex was collected by experienced orthopedic surgeons.

Radiographic assessment. All participants underwent radiographic examination of both knees using an anterior-posterior view with weight-bearing and foot-map positioning. Fluoroscopic guidance with a horizontal anterior-posterior radiograph beam was used to visualize the joint space. Knee radiographs were read by a single experienced orthopedist without knowledge of participants' clinical status, and categorized using the KL grading scale[23]. Regarding the differences in knee OA grades between the 2 sides, among 1681 participants who underwent X-ray examinations of both knees, 1226 (72.9%) individuals had the same KL grades for both knees. For 396 (23.6%) participants, the difference in knee KL grades between the 2 knees was 1, and for the remaining 59 (3.5%) subjects, the KL grades differed by more than 2 grades. In such cases, the higher KL grade was assigned to the participant. The same observer scored 100 randomly selected knee radiographs more than 1 month after the first reading to determine intraobserver variability. The intraobserver variability (0.86) evaluated for KL grade (0–4) was confirmed by kappa analysis to be sufficient for the assessment.

Table 1. Background characteristics of the participants.

	Total	Men	Women
Age, yrs			
≤ 39	45	14	31
40–49	149	44	105
50–59	316	107	209
60–69	482	157	325
70–79	539	220	319
≥ 80	159	54	105
Total, n	1690	596	1094
Mean (SD) selected characteristics			
Age, yrs	65.2 (12.0)	66.3 (11.7)	64.7 (12.1)
Height, cm	155.2 (9.3)	163.4 (7.2)	150.7 (6.9)
Weight, kg	55.6 (10.8)	62.2 (10.9)	52.0 (8.8)
BMI, kg/m^2	23.0 (3.4)	23.2 (3.2)	22.9 (3.5)
Systolic BP, mm Hg	135.1 (20.7)	137.9 (19.6)	133.5 (21.1)
Diastolic BP, mm Hg	74.2 (11.5)	77.0 (11.6)	72.7 (11.2)
Serum levels of HDL cholesterol, mg/dl	60.8 (15.7)	56.1 (15.8)	63.4 (15.0)
Serum levels of HbA1c, %	5.20 (0.74)	5.23 (0.83)	5.19 (0.68)
Prevalence of selected characteristics, %			
Current smoking habit	13.1	29.9	3.8
Current alcohol consumption	39.8	66.7	25.1
Medication for hypertension	32.3	29.5	33.9
Medication for dyslipidemia	6.5	3.0	8.5
Medication for diabetes mellitus (including insulin injection)	5.9	7.7	4.9
Prevalence of each component of metabolic syndrome, %			
Obesity	25.3	26.7	24.6
Hypertension	69.7	74.8	66.9
Dyslipidemia	12.3	13.9	11.4
Impaired glucose tolerance	21.5	24.3	20.0

BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; HbA1c: hemoglobin A1c.

Further, to evaluate the KOA severity using quantitative measurements, the medial and lateral MJSW, medial and lateral JSA, and OPA were measured separately, using a KOA computer-assisted diagnostic system (KOACAD). The KOACAD was programmed to measure MJSW and JSA in the medial and lateral compartments, OPA at the medial tibia, and femorotibial angle (FTA) using digitized knee radiographs. Initially, correction for radiographic magnification was performed on the basis of the image size of a rectangular metal plate.

Next, to determine the region of interest (ROI) including the tibiofemoral joint space, a vertical neighborhood difference filter was applied to identify points with high absolute values for difference of scales. The centers of all points were then calculated, and the ROI was selected. Within the ROI, the outline of the femoral condyle was designated as the upper rim of the joint space. The 2 ends were determined, and vertical lines from the ends were designated as the outside rims of the joint space. Outlines of the anterior and posterior margins of the tibial plateau were drawn similarly to that of the femoral condyle, and the middle line between the 2 outlines was designated as the lower rim of the joint space. A straight regression line for the lower rim outline was then drawn, and the intersection of the lower rim outline and the regression line were designated as the inside rims. Medial and lateral JSA were determined as areas surrounded by the upper, lower, inside, and outside rims. Medial and lateral MJSW were further determined as the minimum vertical distances in the respective JSA. To measure osteophyte area and FTA, medial and lateral outlines of the femur and tibia were drawn. Inflection points for these outlines were then calculated. The medial outline of the tibia from the inflection point was drawn upward to the joint level, and the area that was medially prominent over the smoothly extended outline was designated as the osteophyte area. For FTA, a middle line between the medial and lateral outlines of the femur from the top of the image to the inflection points was drawn, and the straight regression line was determined as the axis of the femur. Similarly, the straight regression line of the middle line of the tibia from the bottom to the inflection points was designated as the axis of the tibia. The lateral angle between the 2 axes lines was calculated as FTA. In general clinical practice, this system can quantify the major features of knee OA on standard radiographs and allows objective, accurate, simple, and easy assessment of the structural severity of knee OA without any manual operation.

Regarding the relationship between the measurements of KOA, we have confirmed the correlation values were more than 0.5 between medial JSA and medial MJSW, and between lateral JSA and lateral MJSW, indicating that these are confounding factors for each other. Osteophyte area was not significantly associated with either medial JSA or medial MJSW. Further, JSA and MJSW on the lateral side were positively correlated with those on the medial side. These measurements showed good correlation between KL grades ($p < 0.0001$)[31].

Blood examination. All blood and urine samples were extracted between 9:00 AM and 3:00 PM. Some samples were extracted under fasting conditions. After centrifugation of blood samples, sera were immediately placed in dry ice and transferred to a deep freezer within 24 hours. These samples were stored at –80°C until assayed.

For the samples of participants in the baseline study, the following items were measured: blood counts, hemoglobin, hemoglobin A1c (HbA1c), blood sugar, total protein, aspartate aminotransferase, alanine aminotransferase, γ-glutamyltranspeptidase, high-density lipoprotein (HDL) cholesterol, total cholesterol, triglycerides (TG), blood urea nitrogen, uric acid, and creatinine. These analyses were performed at the same laboratory within 24 hours after the extraction (Osaka Kessei Research Laboratories Inc., Osaka, Japan).

Definition of MS components. This definition was based mainly on the criteria of the Examination Committee of Criteria for Metabolic Syndrome in Japan[32]. According to these criteria, an abdominal circumference ≥ 85 cm in men and ≥ 90 cm in women is a necessary condition for MS. HTN was diagnosed as systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 85 mm Hg, DL as serum TG level ≥ 150 mg/dl and/or serum HDL cholesterol level < 40 mg/dl, and IGT as fasting serum glucose ≥ 110 mg/dl. Because there has been considerable debate regarding the measurement of abdominal circumference[33,34], we decided to use BMI ≥ 25 instead as an indicator of overweight, based on the criteria of the Japan Society for the Study of Obesity[33]. Also, because not all blood samples were obtained under fasting conditions, we did not use participants' data concerning serum levels of glucose and TG, because of their large variation depending on hours after eating. Instead, we used a serum HDL cholesterol level < 40 mg/dl to indicate DL, and serum HbA1c level ≥ 5.5% to indicate IGT. These are indices used in the National Health and Nutrition Survey in Japan, and they were adopted as criteria for MS in this national screening based on the difficulty of collecting the samples under fasting conditions[35]. Further, subjects being treated with medication for HTN, DL, or diabetes mellitus were regarded as having the respective disorder.

Statistical analysis. All statistical analyses were performed using Stata statistical software (Stata Corp., College Station, TX, USA). Differences in proportion were compared by the chi-squared test. Differences in continuous values were tested for significance using ANOVA for comparisons among multiple groups, and Scheffe's least significant difference test for pairs of groups. Significant items were selected, and multiple regression and logistic regression analyses were performed by adjusting selected variables. Various confounding factors were used for the adjustment for each multivariate analysis.

RESULTS

Study population. Table 1 shows selected characteristics of the participants including age, height, weight, BMI, systolic and diastolic BP, and serum levels of HDL cholesterol and HbA1c, classified by sex. Two-thirds of the 1690 participants were women, and their mean age was 1.5 years younger than that of the men ($p = 0.0098$).

Height, weight, and BMI were significantly lower in women than in men (height, $p < 0.0001$; weight, $p < 0.0001$; BMI, $p = 0.049$). Both measurements of systolic BP and diastolic BP were significantly higher in men than in women (systolic BP and diastolic BP, $p < 0.0001$). However, there was no significant difference in serum levels of HbA1c between men and women ($p = 0.2472$). The serum level of HDL cholesterol was significantly lower in men than in women ($p < 0.0001$).

Table 1 also shows the proportion of subjects who smoked (regularly or more than once a month) and consumed alcohol (drinking regularly or more than once a month); medication use; and the prevalence of OW, HTN, DL, and IGT. Smoking and drinking were significantly more common in men than in women ($p < 0.001$). In the total population, the component of MS with the highest prevalence was HTN, followed by OW, IGT, and DL. The prevalence of HTN and IGT was significantly higher in men than in women (HTN, $p = 0.001$; IGT, $p = 0.039$).

Prevalence of KOA and its association with components for MS. The prevalence of KOA in the total population in the age groups ≤ 39, 40–49, 50–59, 60–69, 70–79, and ≥ 80 years was 2.2%, 10.7%, 28.2%, 50.8%, 69.0%, and 80.5%, respectively. KOA prevalence tended to be higher with increasing age in both the sexes. The prevalence of KOA was significantly higher in women than in men ($p < 0.001$). Table 2 shows the mean values of each component of MS compared between the absence and presence of KOA. In the overall population, mean values of age, BMI, systolic BP, and HbA1c were significantly higher, and HDL cholesterol significantly lower, in subjects with KOA than in those without KOA. This tendency was much more pronounced in women than in men.

Logistic regression analysis was performed using the presence of KOA as an objective variable and OW, HTN, DL, and IGT each as explanatory variables, after adjusting for age and sex. In the overall population, the analysis revealed that only OW was significantly positively associated with KOA (OR 2.33, 95% CI 1.79–3.04, $p < 0.001$). Logistic regression analysis using the same objective and explanatory factors and stratified according to sex indicated that only HTN was positively associated with KOA in men (OR 1.61, 95% CI 1.03–2.53, $p = 0.038$), and only OW in women (OR 3.48, 95% CI 2.42–5.01, $p < 0.001$).

Table 3 shows the prevalence of potential associated lifestyle factors for KOA classified by the absence or presence of KOA. In the overall population, significantly associated factors for KOA included residential area, smoking habit, alcohol consumption, bicycling regularly as a factor of physical activity, and regular exercises. These factors should be taken into consideration as confounders for the following multivariate analysis.

Then, logistic regression analysis was repeated using the presence of KOA as an objective variable and OW, HTN, DL, and IGT each as explanatory variables, after adjusting for age, sex, regional difference, smoking habit, alcohol consumption, physical activities including regular bicycling in the past 12 months, regular exercises such as football, tennis, baseball, and golf; and history of knee injuries. The analysis revealed that OW and HTN were significantly positively associated with KOA (OW: OR 2.74, 95% CI 1.07–3.62, $p < 0.001$; HTN: OR 1.43, 95% CI 1.09–1.86, $p < 0.001$). Logistic regression analysis using the same objective and explanatory factors and stratified according to sex indicated that OW and HTN were positively associated with KOA in men (OW: OR 1.76, 95% CI 1.13–2.74, $p < 0.05$; HTN: OR 1.77, 95% CI 1.11–2.84, $p < 0.05$), and only OW in women (OR 3.63, 95% CI 2.51–5.25, $p < 0.001$). These results suggest that all components of MS were not equally associated with the presence of KOA.

Then, to clarify the association between all the components of MS and KOA, logistic regression analysis was repeated using the presence of KOA as an objective variable and all components for MS, such as OW, HTN, DL, and IGT, as explanatory variables, after adjustment for age, sex, regional difference, smoking habit, alcohol consumption, physical activities, regular exercises, and history of knee injuries. In the overall population, the analysis revealed that

Table 2. Mean (SD) of each component of metabolic syndrome in the absence or presence of knee osteoarthritis (KOA).

	Total			Men			Women		
	KOA–	KOA+	p	KOA–	KOA+	p	KOA–	KOA+	p
Age, yrs	59.8 (12.1)	70.5 (9.1)	0.0001	62.5 (12.1)	71.5 (8.8)	0.0001	57.8 (11.8)	70.3 (9.1)	0.0001
BMI, kg/m^2	22.4 (3.2)	23.5 (3.4)	0.0001	23.0 (3.2)	23.5 (3.2)	0.0931	22.0 (3.1)	23.6 (3.6)	0.0001
Systolic BP, mm Hg	130.7 (19.9)	139.3 (20.7)	0.0001	134.5 (18.9)	142.5 (19.6)	0.0001	127.9 (20.0)	138.0 (21.0)	0.0001
Diastolic BP, mm Hg	74.2 (11.2)	74.2 (11.8)	0.9890	77.1 (11.6)	76.8 (11.5)	0.6970	72.1 (10.4)	73.1 (11.8)	0.1380
Serum levels of HDL cholesterol, mg/dl	62.8 (16.6)	58.9 (14.5)	0.0001	57.5 (16.2)	54.1 (15.0)	0.0095	6.6 (15.8)	60.8 (13.9)	0.0001
Serum levels of HbA1c, %	5.13 (0.68)	5.26 (0.78)	0.0003	5.22 (0.83)	5.23 (0.80)	0.9409	5.07 (0.53)	5.28 (0.77)	0.0001

BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; HbA1c: hemoglobin A1c.

Table 3. Prevalence (%) of portential associated factors for knee osteoarthritis (KOA) classified by the absence or presence of KOA.

	Total			Men			Women		
	KOA–	KOA+	p	KOA–	KOA+	p	KOA–	KOA+	p
Residing in coastal area	65.6	32.1	0.000	60.8	26.7	0.000	69.0	34.3	0.000
Current smoking	16.7	9.5	0.000	34.7	23.5	0.012	3.92	3.53	0.060
Current alcohol drinking	46.2	33.4	0.000	68.1	65.3	0.475	30.8	20.2	0.000
Bicycling every day in the past 12 mo	52.6	59.3	0.006	55.1	55.1	0.998	50.8	61.0	0.001
Regular exercise such as football, tennis, baseball, and golf	18.3	10.6	0.000	34.9	30.0	0.209	6.53	2.51	0.001
Past injury of either knee	2.4	2.8	0.560	1.4	4.1	0.046	3.1	2.4	0.466

OW was significantly positively associated with KOA (OR 2.65, 95% CI 1.98–3.54, $p < 0.001$). Logistic regression analysis using the same objective and explanatory factors and stratified according to sex indicated that, in both sexes, OW was the only factor that was significantly associated with KOA (men: OR 1.64, 95% CI 1.04–2.59, $p < 0.05$; women: OR 3.64, 95% CI 2.48–5.34, $p < 0.001$), while in men, there was weak but not significant association between HTN and KOA (OR 1.61, 95% CI 0.99–2.60, $p = 0.053$). These results suggest that obesity, among the various components for MS, was most significantly correlated to KOA.

Prevalence of KOA and its association with the number of components for MS. Table 4 shows the prevalence of KOA classified by the number of components for MS: the prevalence of KOA tended to increase with the increase in the number of MS components (p for trend < 0.001) in the total population. However, the prevalence of KOA in men and women did not tend to increase monotonically. Thus, in men, the prevalence of KOA in the groups with 2 MS components was lower than that in the groups with 1 component. Similarly, in women, the prevalence of KOA in the group with 2 MS components was higher than that in the group with 3 or more components.

To clarify the effect of the accumulation of MS components on the presence of KOA, logistic regression analysis was performed using the presence of KOA as the objective variable and the MS components (OW, HTN, DL, and IGT) present as explanatory variables after adjustment for age and sex. Compared to the reference condition (no MS components), increasing the number of components of MS significantly increased the OR for the presence of KOA (vs no component; 1 component: OR 1.18, 95% CI 0.87–1.61, $p = 0.273$; 2 components: OR 1.74, 95% CI 1.25–2.44, $p = 0.001$; more than 3 components: OR 2.15, 95% CI 1.44–3.23; $p < 0.001$). Again, the same analysis was also performed stratified by sex. In men, although no dose-response effects of the accumulation of MS components on KOA were observed when the number of the components was 1 or 2, the accumulation of 3 or more components of MS tended to be significantly associated with a higher OR of KOA (vs no component; 1 component: OR 1.94, 95% CI 1.11–3.39, $p = 0.021$; 2 components: OR 1.61, 95% CI 0.89–2.91, $p = 0.117$; more than 3 components: OR 2.96, 95% CI 1.5–5.85, $p = 0.002$). In contrast, in women, no significant difference was observed between the presence of no components and 1 component; however, 2 or more components of MS increased the risk of KOA significantly (vs no component; 1 component: OR 0.89, 95% CI 0.61–1.29, $p = 0.527$; 2 components: OR 1.94, 95% CI 1.27–2.96, $p = 0.002$; more than 3 components: OR 1.71, 95% CI 1.01–2.87, $p = 0.044$).

Logistic regression analysis was performed using the presence of KOA as the objective variable and the number of MS components present (OW, HTN, DL, and IGT) as explanatory variables, after adjustment for age, sex, regional difference, smoking habit, alcohol consumption, physical activities, regular exercises, and history of knee injuries. Figure 1 shows the OR of the association between accumulation of components of MS and presence of KOA. Compared to the reference condition (no components of MS), increasing the number of components of MS significantly increased the OR for the presence of KOA (vs no component; 1 component: OR 1.21, 95% CI 0.88–1.68, $p = 0.237$; 2 components: OR 1.89, 95% CI 1.33–2.70, $p < 0.001$; > 3 components: OR 2.72, 95% CI 1.77–4.18, $p < 0.001$). Again, the same analysis was also performed stratified by sex. In men, although no dose-response effects of the accumulation of MS components on KOA were observed when the number of the components was 1 or 2, the accumulation of 3 or more components of MS tended to be significantly associated with a higher OR of KOA (vs no com-

Table 4. Prevalence (%) of knee osteoarthritis, classified by the number of components of metabolic syndrome (MS). MS components consisted of obesity, hypertension, dyslipidemia, and impaired glucose tolerance.

No. MS Components	Total	Men	Women
0	32.5	24.8	35.4
1	49.9	44.8	52.9
2	60.5	42.7	71.8
≥ 3	62.2	51.3	69.4

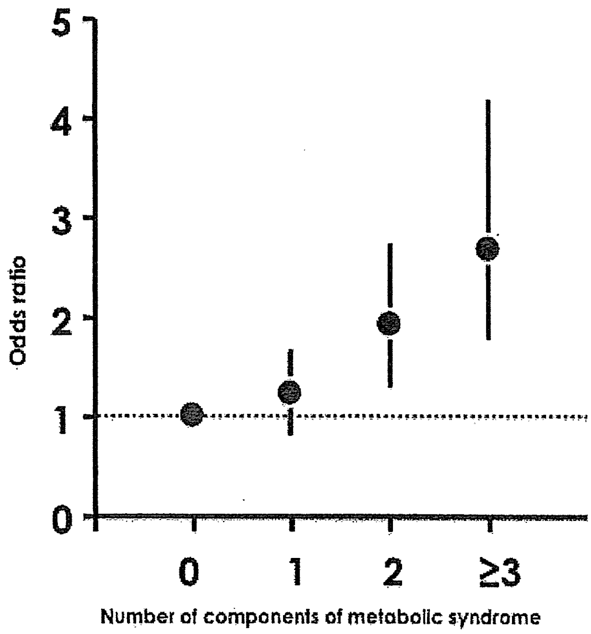

Figure 1. Odds ratios of the association between the number of components of metabolic syndrome and the presence of knee osteoarthritis, compared to no components present.

ponent; 1 component: OR 2.07, 95% CI 1.15–3.74, p = 0.016; 2 components: OR 1.68, 95% CI 0.89–3.17, p = 0.110; more than 3 components: OR 3.88, 95% CI 1.87–80.6, $p < 0.001$). In contrast, in women, no significant difference was observed between the presence of no component and 1 component; however, 2 or more components of MS increased the OR of KOA significantly (vs no component; 1 component: OR 0.88, 95% CI 0.59–1.32, p = 0.541; 2 components: OR 2.13, 95% CI 1.36–3.34, p = 0.001; > 3 components: OR 2.17, 95% CI 1.25–3.77, p = 0.006).

Joint space narrowing and areas of osteophytes in the knee, and their association with components of MS. Tables 5A and 5B show the mean measurements of indices for KOA, medial MJSW (mm), lateral MJSW (mm), medial JSA (mm^2), lateral JSA (mm^2), and OPA (mm^2), classified by the number of components of MS. The values of medial MJSW tended to be significantly lower, and those of OPA significantly higher, with the increasing number of components of MS. The values of medial JSA in women belonging to the group with no component of MS were significantly higher than in those belonging to the groups with 1, 2, 3, or more components of MS, but no such tendency was observed in men. There was no relationship between the values of lateral MJSW, lateral JSA, and the number of components of MS.

Multiple regression analysis was performed using values of medial MJSW as the objective variable and the number of components of MS present as explanatory variables, after adjustment for age, sex, regional difference, smoking habit, alcohol consumption, physical activities, regular exercises, and history of knee injuries. In the overall population, we found that the number of components of MS was inversely related to the values of medial MSJW (ß = –0.148, R^2 = 0.21, $p < 0.001$). An analysis performed using the same objective and explanatory factors and stratified by sex showed the same tendency in both men and women (men: ß = –0.152, R^2 = 0.14, $p < 0.001$; women: ß = –0.149, R^2 = 0.18, $p < 0.001$).

Multiple regression analysis was then performed using OPA values as the objective variable and the number of components of MS present as explanatory variables, after adjustment for age, sex, regional difference, smoking habit, alcohol consumption, physical activities, regular exercises, and history of knee injuries. The analysis revealed that the number of components of MS was positively related to OPA values (ß = 0.12, R^2 = 0.11, $p < 0.001$). An analysis performed using the same objective and explanatory factors and stratified by sex showed the same tendency in both men and women (men: ß = 0.15, R^2 = 0.08, $p < 0.001$; women: ß = 0.11, R^2 = 0.11, $p < 0.001$).

In women, multiple regression analysis was performed using values of medial JSA as the objective variable and the number of components of MS present as explanatory variables, after adjustment for age, regional difference, smoking habit, alcohol consumption, physical activities, regular exercises, and history of knee injuries. The analysis revealed that the number of components of MS was inversely related to the values of medial JSA in women (ß = –0.096, R^2 = 0.18, p = 0.001).

DISCUSSION

We found that an increase in the number of components of MS was significantly associated with the presence of KOA diagnosed by using the KL scale in Japanese men and women. We also clarified that the values of medial MJSW and OPA in men and women, and medial JSA in women as features of KOA, were significantly associated with the increase in the number of MS components.

KOA and MS share age and OW as risk factors[1,7,8,9,10,11]. We have already reported that higher BMI was associated with radiographic KOA based on an analysis using the same population evaluated in our study[36], and it was also clarified that OW was the strongest factor that influenced the prevalence of KOA.

Regarding the association between clustering of metabolic factors and KOA, Hart, *et al* found that metabolic factors including blood glucose, hypercholesterolemia, and HTN were associated with both unilateral and bilateral KOA and were independent of OW[20]. Sowers, *et al*[21] defined the presence of ≥ 2 of the following criteria as cardiometabolic clustering: low levels of HDL cholesterol, elevated levels of low-density lipoprotein cholesterol, TG, BP, C-reactive protein, waist/hip ratio, glucose levels, and dia-

Table 5A. Mean (SD) of medial and lateral minimum joint space width (MJSW) classified by the number of components of metabolic syndrome (MS). MS components consisted of obesity, hypertension, dyslipidemia, and impaired glucose tolerance.

No. MS Components	Medial MJSW, mm Total	Medial MJSW, mm Men	Medial MJSW, mm Women	Lateral MJSW, mm Total	Lateral MJSW, mm Men	Lateral MJSW, mm Women
0	2.98 (0.81)	3.33 (0.66)	2.85 (0.82)	4.00 (1.18)	4.37 (1.13)	3.86 (1.17)
1	2.69 (1.01)[a]	3.05 (0.97)	2.49 (0.98)[a]	3.96 (1.13)	4.43 (1.05)	3.70 (1.08)
2	2.43 (1.19)[ab]	2.87 (1.10)[a]	2.15 (1.17)[ab]	3.85 (1.19)	4.15 (1.10)	3.66 (1.22)
≥ 3	2.42 (1.22)[ab]	2.73 (1.24)[a]	2.22 (1.17)[a]	4.06 (1.27)	4.26 (1.29)	3.93 (1.24)

[a] Significantly different from values obtained in the absence of components ($p < 0.05$). [b] Significantly different from values obtained with 1 component ($p < 0.05$).

Table 5B. Mean (SD) of medial and lateral joint space area (JSA) and area of osteophytosis (OPA), classified by number of components of metabolic syndrome (MS). MS components consisted of obesity, hypertension, dyslipidemia, and impaired glucose tolerance.

No. MS Components	Medial JSA, mm² Total	Medial JSA, mm² Men	Medial JSA, mm² Women	Lateral JSA, mm² Total	Lateral JSA, mm² Men	Lateral JSA, mm² Women	OPA, mm² Total	OPA, mm² Men	OPA, mm² Women
0	96.3 (27.6)	111.4 (25.6)	98.8 (26.2)	111.0 (33.2)	132.2 (34.2)	103.3 (29.2)	1.81 (6.42)	0.93 (2.97)	2.13 (7.26)
1	90.2 (31.7)[a]	104.0 (30.7)	82.3 (29.6)[a]	111.0 (32.4)	131.2 (30.5)	99.5 (27.5)	3.06 (7.89)	1.33 (4.26)	4.05 (9.21)
2	85.2 (36.7)[a]	101.1 (34.3)	75.0 (34.6)[ab]	111.7 (32.2)	128.9 (29.6)	100.6 (28.8)	5.34 (11.25)[ab]	2.45 (5.36)	7.18 (13.44)[ab]
≥ 3	88.2 (39.3)	102.0 (40.1)	79.1 (36.0)[a]	118.2 (35.3)	132.5 (34.7)	108.8 (32.5)[b]	6.26 (9.59)[ab]	3.82 (8.70)[ab]	7.86 (9.85)[ab]

[a] Significantly different from values obtained in the absence of components ($p < 0.05$). [b] Significantly different from values obtained with 1 component ($p < 0.05$).

betes mellitus, and assessed the association between cardiometabolic clustering and KOA. They found that KOA was significantly more frequent in obese women with cardiometabolic clustering compared with those without it[21]. Using data from the National Health and Nutrition Examination Survey III (NHANES III), Singh, *et al* suggested that adults with OA in the United States have a high prevalence of CVD risk factors[19], and Puenpatom and Victor demonstrated that each of the 5 cardiovascular risk factors that comprise MS, HTN, abdominal OW, hyperglycemia, elevated TG, and low HDL cholesterol, was more prevalent in the population with OA than in the population without OA[22]. However, to our knowledge, few population-based studies have shown a dose-response relationship between the presence of KOA and the accumulation of the number of MS components.

In our study, the logistic regression analysis revealed that only OW was significantly associated with KOA, and other components were not significant, using the presence of KOA as an objective variable and all components for MS, such as OW, HTN, DL, and IGT as explanatory variables and after adjustment for potential confounders. However, we found that the higher the number of components of MS, the greater the OR of the presence of KOA. This result indicates that, even if the effect of each component of MS on KOA may be weak, accumulation of the number of components may significantly worsen KOA.

In addition, we found that medial MJSW values in men and women, and medial JSA values in women tended to be significantly lower with the increase in the number of components of MS. In contrast, OPA values became significantly higher with the increase in the number of components of MS. Regarding the association between JSW and KOA, Sowers, *et al* used statistical models that included variables representing obesity, cardiometabolic status, and lateral and medial JSW differences to show that a 1-mm increase in the difference between lateral and medial JSW was associated with 2.1 times greater odds of having KOA, and subjects who were obese with cardiometabolic clustering had 4.5 times greater odds of having KOA[21]. However, no other reports have addressed direct associations between indices of KOA, such as MJSW, JSA, and OPA values, with the accumulation of the number of components of MS. In our study, we confirmed that the accumulation of the number of MS components present influenced the values of both MJSW, JSA (women only), and OPA, which determine the features and severity of KOA.

Regarding the association of clustering of components for MS and KOA, a few hypotheses have been suggested. Hart, *et al* attributed the effect of excess endogenous estrogens to the aromatization of estrone in fat tissue[20]. Regarding the endogenous secreted products, Sowers, *et al* suggested that leptin and adiponectin levels influenced the development of OA[21]. They stated that leptin concentrations in the synovial fluid of patients with OA correlated with their BMI, and levels of adiponectin are low in obese individuals and in those with CVD. Another hypothesis states that atherosclerotic change may play a role in the development of OA. Kornaat, *et al* reported the association between increased popliteal artery vessel wall thickness and generalized OA[37]. It has been hypothesized that atherosclerotic changes and obesity-associated metabolic changes in the subchondral bone are associated with OA[37,38]. In obese subjects, metabolic changes in the striated muscles induced by the interaction of insulin resistance and systemic inflammation might lead to fatigue and muscle weakness, which influences the balance between damage and repair mechanisms leading to OA[37,39]. In our study, we could not substantiate these hypotheses because of the lack of relevant measurements. However, in the followup study, we will obtain the ankle brachial pressure index and pulse wave velocity of the ROAD subjects, and thus we will further the evidence regarding the association between arteriosclerosis and KOA.

In our study, a sexual dimorphism pattern was shown in prevalence of KOA (women > men) and components of MS such as values of BMI (men > women), BP (men > women), and HDL cholesterol (women > men). Regarding KOA, being female is well known as a strong risk factor, according to our previous survey and other studies[27,40,41,42,43,44], possibly implicating an involvement of muscle strength to compensate for the mechanical stress, since women are known to have less muscle strength than men[45]. Sex differences in the prevalence of MS might be partly explained by endogenous sex steroids. As mentioned, Hart, *et al* attributed the effect of excess endogenous estrogens to the aromatization of estrone in fat tissue[20]. Recent systematic review and metaanalysis of observational studies concluded that there is a sex-dependent association between levels of testosterone and occurrence of MS[46]. In addition, the difference in prevalence of associated confounding factors may influence the effect of sex difference on the occurrence of MS. In our study, there are sex differences in lifestyle-related factors, which might influence the occurrence of MS. For example, the proportions of smokers and alcohol consumers are both significantly higher in men than in women (both $p < 0.001$). Regarding the physical activities, the proportion of men who exercised regularly was significantly higher than that of women ($p < 0.001$). Therefore, for the statistical analyses, we adjusted not only for age and sex, but also for such potentially confounding factors to show the association between components of MS and KOA.

With regard to ethnic differences in MS, Hoang, *et al* reviewed epidemiological studies and reported that the prevalence of MS in East Asians was lower than that in whites[28]. However, the prevalence of MS may increase rapidly. Nestel reported a dramatic increase in the prevalence of MS in a cohort from Beijing, from 9% to 21%, between 1992 and 2002[47]. In addition, as reported, the prevalence of KOA in Japanese as well as Chinese cohorts is significantly higher than in whites[27,36]. In light of the rapidly increasing population in Asian countries, prevention strategies for obesity-related chronic diseases, such as MS and KOA, should be implemented immediately. In our study, we clarified that components of MS and their accumulation were associated with KOA in Asian subjects. Based on these findings, the prevention of MS may be useful in the prevention of not only CVD, but also KOA, in both Asian and Western countries, and may lead to a reduction in the number of patients who have a disability arising from joint disorders.

There are several limitations in our study. First, although the ROAD study includes a large number of participants, these participants may not be truly representative of the general population. To confirm whether the participants of the ROAD study are representative of the Japanese population, we compared anthropometric measurements and the frequencies of smoking and alcohol consumption between study participants and the general Japanese population, and no significant differences were found, except that male ROAD study participants aged 70–74 years were significantly smaller in terms of body structure than the overall Japanese population ($p < 0.05$)[29]. This difference should be considered when evaluating the potential risk factors for men aged 70–74 years; factors such as body build, particularly heavy weight, are known to be associated with the presence of MS and KOA. Thus, our results might represent an underestimation. Second, this was a cross-sectional study, and the causal relationship between metabolic factors and KOA remains unclear. Metabolic factors may have changed recently or been longstanding; this can only be ascertained by a longitudinal study that clarifies the incidence and/or progression rates of KOA in the same cohort. The first such followup of the ROAD cohort is in progress; it intends to clarify the causal relationships between musculoskeletal diseases and MS for early prevention of the disabilities. Third, we categorized MS by using the criteria defined by the Examination Committee of Criteria for Metabolic Syndrome in Japan[29], except for the definition of overweight. We used BMI ≥ 25 as the criterion for OW status, as defined by the Japan Society for the Study of Obesity[30]. In addition, since the blood samples obtained were not always from participants under fasting conditions, we used serum HDL cholesterol level < 40 mg/dl to indicate DL, and serum HbA1c level ≥ 5.5% to indicate IGT, which are indices used by the National Health and Nutrition Survey in Japan[32]. These differences in the definition of MS may skew the true association between MS and KOA. However, our aim was to determine how the accumulation of MS components was related to KOA, and we believe the indices we used for OW, HTN, DL, and IGT accurately reflected the participants' physical condition.

Our study evaluated a large-scale population from the

ROAD study and revealed that the presence of KOA was significantly associated with increases in the number of components of MS. Additionally, the number of components of MS was inversely related to medial MSJW values and positively related to OPA values. The prevention of MS may be useful for both CVD and KOA in Asian populations. Further investigations, along with continued longitudinal surveys in the ROAD study, will elucidate the components of MS and occurrence or progress of KOA.

REFERENCES

1. Sharma L, Kapoor D. Epidemiology of osteoarthritis. In: Moskowitz RW, Altman RD, Hochberg MC, Buckwalter JA, Goldberg VM, editors. Osteoarthritis: diagnosis and medical/surgical management. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2007:3-26.
2. Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health 1994;84:351-8.
3. Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. Arthritis Rheum 1998;41:1343-55.
4. Ministry of Health, Labour and Welfare, Japan. The outline of the results of National Livelihood Survey 2007 [Japanese]. [Internet. Accessed January 7, 2011.] Available from: http://www.mhlw.go.jp/toukei/list/20-19-1.html
5. Dahlöf B. Cardiovascular disease risk factors: epidemiology and risk assessment. Am J Cardiol 2010;105:3A-9A.
6. Day C. Metabolic syndrome, or what you will: definitions and epidemiology. Diab Vasc Dis Res 2007;4:32-8.
7. Felson DT, Anderson JJ, Naimark A, Walker WM, Meenan RF. Obesity and knee osteoarthritis: the Framingham Study. Ann Intern Med 1988;109:18-24.
8. Hart DJ, Spector TD. The relationship of obesity, fat distribution and osteoarthritis in the general population: the Chingford Study. J Rheumatol 1993;20:331-5.
9. Van Saase JL, Vandenbroucke JP, Van Romunde LK, Valkenburg HA. Osteoarthritis and obesity in the general population. A relationship calling for an explanation. J Rheumatol 1998; 15:1152-8.
10. Magliano M. Obesity and arthritis. Menopause Int 2008;14:149-54.
11. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis. Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008;16:137-62.
12. Lawrence JS. Hypertension in relation to musculoskeletal disorders. Ann Rheum Dis 1975;34:451-6.
13. Kellgren JH. Osteoarthritis in patients and populations. BMJ 1961;1:1-6.
14. Cimmino MA, Cutolo M. Plasma glucose concentration in symptomatic osteoarthritis: a clinical and epidemiological survey. Clin Exp Rheumatol 1990;8:251-7.
15. Davis MA, Ettinger WH, Neuhaus JM. The role of metabolic factors and blood pressure in the association of obesity with osteoarthritis of the knee. J Rheumatol 1988;15:1827-32.
16. Cooper C, McAlindon T, Snow S, Vines K, Young P, Kirwan J, et al. Mechanical and constitutional risk factors for symptomatic knee osteoarthritis: differences between medial tibiofemoral and patellofemoral disease. J Rheumatol 1994;21:307-13.
17. Martin K, Lethbridge-Cejku M, Muller DC, Elahi D, Andres R, Tobin JD, et al. Metabolic correlates of obesity and radiographic features of knee osteoarthritis: data from the Baltimore Longitudinal Study of Aging. J Rheumatol 1997;24:702-7.
18. Stürmer T, Brenner H, Brenner RE, Günther KP. Non-insulin dependent diabetes mellitus (NIDDM) and patterns of osteoarthritis. The Ulm osteoarthritis study. Scand J Rheumatol 2001;30:169-71.
19. Singh G, Miller JD, Lee FH, Pettitt D, Russell MW. Prevalence of cardiovascular disease risk factors among US adults with self-reported osteoarthritis: data from the Third National Health and Nutrition Examination Survey. Am J Manag Care 2002;8:S383-91.
20. Hart DJ, Doyle DV, Spector TD. Association between metabolic factors and knee osteoarthritis in women: the Chingford study. J Rheumatol 1995;22:1118-23.
21. Sowers M, Karvonen-Gutierrez CA, Palmieri-Smith R, Jacobson JA, Jiang Y, Ashton-Miller JA. Knee osteoarthritis in obese women with cardiometabolic clustering. Arthritis Rheum 2009;61:1328-36.
22. Puenpatom RA, Victor TW. Increased prevalence of metabolic syndrome in individuals with osteoarthritis: an analysis of NHANES III data. Postgrad Med 2009;121:9-20.
23. Kellgren JH, Lawrence LS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494-502.
24. Jones G, Ding C, Scott F, Glisson M, Cicuttini F. Early radiographic osteoarthritis is associated with substantial changes in cartilage volume and tibial bone surface area in both males and females. Osteoarthritis Cartilage 2004;12:169-74.
25. Yamada T, Kawano H, Koshizuka Y, Fukuda T, Yoshimura K, Kamekura S, et al. Carminerin contributes to chondrocyte calcification during endochondral ossification. Nat Med 2006;12:665-70.
26. Kamekura S, Kawasaki Y, Hoshi K, Shimoaka T, Chikuda H, Maruyama Z, et al. Contribution of runt-related transcription factor 2 to the pathogenesis of osteoarthritis in mice after induction of knee joint instability. Arthritis Rheum 2006;54:2462-70.
27. 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 Cartilage 2009;17:1137-43.
28. Hoang KC, Le TV, Wong ND. The metabolic syndrome in East Asians. J Cardiometab Syndr 2007;2:276-82.
29. Yoshimura N, Muraki S, Oka H, Mabuchi 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 Study. J Bone Miner Metab 2009;27:620-8.
30. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T. Cohort profile: Research on Osteoarthritis/Osteoporosis Against Disability Study. Int J Epidemiol 2010;39:988-95.
31. Oka H, Muraki S, Akune T, Mabuchi A, Suzuki T, Yoshida H, et al. Fully automatic quantification of knee osteoarthritis severity on standard radiographs. Osteoarthritis Cartilage 2008;16:1300-6.
32. The Examination Committee of Criteria for Metabolic Syndrome. The definition and criteria of metabolic syndrome [Japanese]. J Jpn Soc Intern Med 2005;94:794-809.
33. Examination Committee of Criteria for 'Obesity Disease' in Japan; Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. Circ J 2002;66:987-92.
34. Shibata K, Suzuki S, Sato J, Ohsawa I, Goto S, Hashiguchi M, et al. Abdominal circumference should not be a required criterion for the diagnosis of metabolic syndrome. Environ Health Prev Med 2010;15:229-35.
35. Ministry of Health, Labour and Welfare. The outline of the results of National Health and Nutrition Survey 2008 [Japanese]. [Internet. Accessed January 7, 2011.] Available from: http://www.mhlw.go.jp/houdou/2009/11/dl/h1109-1b.pdf
36. Muraki S, Akune T, Oka H, Mabuchi A, En-yo Y, Yoshida M, et al. Association of occupational activity with radiographic knee

osteoarthritis and lumbar spondylosis in elderly patients of population-based cohorts: a large-scale population-based study. Arthritis Rheum 2009;61:779-86.
37. Kornaat PR, Sharma R, van der Geest RJ, Lamb HJ, Kloppenburg M, Hellio le Graverand MP, et al. Positive association between increased popliteal artery vessel wall thickness and generalized osteoarthritis: is OA also part of the metabolic syndrome? Skeletal Radiol 2009;38:1147-51.
38. Conaghan PG, Vanharanta H, Dieppe PA. Is progressive osteoarthritis an atheromatous vascular disease? Ann Rheum Dis 2005;64:1539-41.
39. Rojas-Rodríguez J, Escobar-Linares LE, Garcia-Carrasco M, Escárcega RO, Fuentes-Alexandro S, Zamora-Ustaran A. The relationship between the metabolic syndrome and energy-utilization deficit in the pathogenesis of obesity-induced osteoarthritis. Med Hypotheses 2007;69:860-8.
40. Kellgren JH, Lawrence JS. Osteo-arthrosis and disk degeneration in an urban population. Ann Rheum Dis 1958;17:388-97.
41. Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. Arthritis Rheum 1987;30:914-8.
42. Anderson JJ, Felson DT. Factors associated with osteoarthritis of the knee in the first national Health and Nutrition Examination Survey (HANES I). Evidence for an association with overweight, race, and physical demands of work. Am J Epidemiol 1988;128:179-89.
43. van Saase JL, van Romunde LK, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. Ann Rheum Dis 1989;48:271-80.
44. Dillon CF, Rasch EK, Gu Q, Hirsch R. Prevalence of knee osteoarthritis in the United States: arthritis data from the Third National Health and Nutrition Examination Survey 1991-94. J Rheumatol 2006;33:2271-9.
45. Sinaki M, Nwaogwugwu NC, Phillips BE, Mokri MP. Effect of gender, age, and anthropometry on axial and appendicular muscle strength. Am J Phys Med Rehabil 2001;80:330-8.
46. Brand JS, van der Tweel I, Grobbee DE, Emmelot-Vonk MH, van der Schouw YT. Testosterone, sex hormone-binding globulin and the metabolic syndrome: a systematic review and meta-analysis of observational studies. Int J Epidemiol 2010 Sep 24 [E-pub ahead of print].
47. Nestel P. Nutritional aspects in the causation and management of the metabolic syndrome. Endocrinol Metab Clin North Am 2004;33:483-92.

Author's personal copy

Osteoarthritis and Cartilage 19 (2011) 840–846

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Association of occupational activity with joint space narrowing and osteophytosis in the medial compartment of the knee: the ROAD study (*OAC5914R2*)

S. Muraki †*, H. Oka ‡, T. Akune †, Y. En-yo §, M. Yoshida §, K. Nakamura ||, H. Kawaguchi ||, N. Yoshimura ‡

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

ARTICLE INFO

Article history:
Received 7 September 2010
Accepted 22 March 2011

Keywords:
Osteoarthritis
Knee
Occupation
Cohort
Epidemiology

SUMMARY

Objective: We investigated the association of occupational activity with joint space narrowing and osteophytosis at the knee separately in Japanese subjects using a large-scale population-based cohort of the Research on Osteoarthritis Against Disability (ROAD).

Methods: From the baseline survey of the ROAD study, 1,402 participants (512 men and 890 women) living in mountainous and seacoast communities were analyzed. Information collected included a lifetime occupational history and details of specific workplace physical activities. To estimate the severity of joint space narrowing and osteophytosis at the knee, minimum joint space width (mJSW) and osteophyte area (OPA) in the medial compartment of the knee were measured using a knee osteoarthritis (OA) computer-aided diagnosis system.

Results: For women, agricultural, forestry, and fishery workers had significantly lower mJSW values compared with clerical workers or technical experts, whereas OPA did not differ significantly among job titles in men or women. For occupational activities, kneeling and squatting were associated with lower mJSW as well as higher OPA. Walking and heavy lifting were associated with lower mJSW, but not with OPA.

Conclusion: This cross-sectional study using a population-based cohort suggests that an occupational activity that includes kneeling and squatting appears to have a greater effect on knee OA.

© 2011 Osteoarthritis Research Society International. Published by Elsevier Ltd. All rights reserved.

Introduction

Knee osteoarthritis (OA), which causes cartilage degeneration and osteophyte formation at joints in the limbs, is a major public health issue causing chronic disability in the elderly in developed countries[1–3]. The prevalence of knee OA is high in the elderly in Japan[4] and 25,300,000 subjects aged 40 years and older are estimated to experience radiographic knee OA[5]. Further, 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 regard to activities of daily living[6].

Established risk factors for knee OA in Caucasians include older age, female sex, evidence of OA in other joints, obesity, and previous injury or surgery of the knee[7–11]. Evidence is accumulating in Caucasians that the disease is more common in people who have performed heavy physical work[12–17], particularly in those whose jobs have involved kneeling or squatting[18–24]. We also showed that occupational activities that included sitting, standing, walking, climbing, and heavy lifting had a significant association with moderate knee OA, and kneeling and squatting were associated with severe knee OA[25]. However, in our and other studies regarding occupational risks for knee OA, the disease was defined according to the Kellgren–Lawrence (KL) grade[26] or whether subjects had undergone total knee arthroplasty. KL grade is the most conventional system to grade radiographic severity of knee OA, but in this categorical system, joint space narrowing and osteophyte formation are not assessed separately. In addition, because the KL system emphasizes osteophytosis, it is unclear how to handle knee OA with joint space narrowing but no osteophytosis. Further, we have already reported that occupational activities of

* Address correspondence and reprint requests to: S. Muraki, Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, Faculty of Medicine, 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 © 2011 Osteoarthritis Research Society International. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.joca.2011.03.008