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 (β = –0.148, R² = 0.21, p < 0.001), medial JSA (women only; β = –0.096, R² = 0.18, p = 0.001), and positively related to OPA (β = 0.12, R² = 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 RISK FACTORS METABOLIC SYNDROME KNEE OSTEOARTHRITIS 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. 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 longer term care.

In the same report, cardiovascular disease (CVD) is...
ranked first in causing disabilities in the elderly\textsuperscript{4}. Most individuals who develop CVD have multiple risk factors\textsuperscript{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)\textsuperscript{6}.

Knee OA (KOA) and MS share age and obesity as risk factors\textsuperscript{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\textsuperscript{12}. Regarding DL, Kellgren reported a significant association between women with hand OA and above-average serum cholesterol levels in the 1960s\textsuperscript{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\textsuperscript{14}. Although contradictory findings regarding the association of such metabolic factors with OA have been reported\textsuperscript{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\textsuperscript{20}. This hypothesis has been supported by data from several population-based studies performed in the United States\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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.
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 (KOA-CAD). The KOACAD was programmed to measure MJSW and JSA in 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. Further, JSA and MJSW on the lateral side were positively correlated with the inflection points was designated as the osteophyte area. 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.

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 drawn similarly to that of the femoral condyle, and the middle line between the 2 outlines 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.

Table 1 shows selected characteristics of the participants including age, height, weight, BMI, systolic blood pressure, fasting glucose, HDL cholesterol, triglyceride, and impaired glucose tolerance. The prevalence of each component of metabolic syndrome is also presented. The prevalence of MS was high in both men and women, and the differences between men and women were statistically significant (p < 0.05). The prevalence of obesity, hypertension, and IGT was also high in both men and women, and the differences between men and women were statistically significant (p < 0.05).

**Definition of MS components.** This definition was based mainly on the criteria of the Examination Committee of Criteria for Metabolic Syndrome in Japan32. 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, based on data of the 2011 guidelines. Impaired glucose tolerance (IGT) was diagnosed as fasting serum glucose ≥ 110 mg/dl. These are indices that have been recommended by the Japan Society for the Study of Obesity33. Also, because not all blood samples were obtained under fasting conditions, we used a serum HDL cholesterol level < 40 mg/dl to indicate IGT. These are indices useful for the diagnosis of MS as defined by the Japan Society for the Study of Obesity33. Further, subjects being treated with medication for HTN, DL, or diabetes mellitus were regarded as having the respective disorder.
The 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). 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).

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, sex, and all components for MS, such as 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 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).

<table>
<thead>
<tr>
<th></th>
<th>KOA−</th>
<th>Total</th>
<th>p</th>
<th>KOA−</th>
<th>Men</th>
<th>KOA+</th>
<th>p</th>
<th>KOA−</th>
<th>Women</th>
<th>KOA+</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>59.8 (12.1)</td>
<td>70.5 (9.1)</td>
<td>0.0001</td>
<td>62.5 (12.1)</td>
<td>71.5 (8.8)</td>
<td>0.0001</td>
<td>57.8 (11.8)</td>
<td>70.3 (9.1)</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.4 (3.2)</td>
<td>23.5 (3.4)</td>
<td>0.0001</td>
<td>23.0 (3.2)</td>
<td>23.5 (3.2)</td>
<td>0.0931</td>
<td>22.0 (3.1)</td>
<td>23.6 (3.6)</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>130.7 (19.9)</td>
<td>139.3 (20.7)</td>
<td>0.0001</td>
<td>134.5 (18.9)</td>
<td>142.5 (19.6)</td>
<td>0.0001</td>
<td>127.9 (20.0)</td>
<td>138.0 (21.0)</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>74.2 (11.2)</td>
<td>74.2 (11.8)</td>
<td>0.9890</td>
<td>77.1 (11.6)</td>
<td>76.8 (11.5)</td>
<td>0.6970</td>
<td>72.1 (10.4)</td>
<td>73.1 (11.8)</td>
<td>0.1380</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum levels of HDL cholesterol, mg/dl</td>
<td>62.8 (16.6)</td>
<td>58.9 (14.5)</td>
<td>0.0001</td>
<td>57.5 (16.2)</td>
<td>54.1 (15.0)</td>
<td>0.0095</td>
<td>6.6 (15.8)</td>
<td>60.8 (13.9)</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum levels of HbA1c, %</td>
<td>5.13 (0.68)</td>
<td>5.26 (0.78)</td>
<td>0.0003</td>
<td>5.22 (0.83)</td>
<td>5.23 (0.80)</td>
<td>0.9409</td>
<td>5.07 (0.53)</td>
<td>5.28 (0.77)</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; HbA1c: hemoglobin A1c.
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 1.94, 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 3. Prevalence (%) of potential associated factors for knee osteoarthritis (KOA) classified by the absence or presence of KOA.

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

### 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.

<table>
<thead>
<tr>
<th>No. MS Components</th>
<th>Total</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>32.5</td>
<td>24.8</td>
<td>35.4</td>
</tr>
<tr>
<td>1</td>
<td>49.9</td>
<td>44.8</td>
<td>52.9</td>
</tr>
<tr>
<td>2</td>
<td>60.5</td>
<td>42.7</td>
<td>71.8</td>
</tr>
<tr>
<td>≥ 3</td>
<td>62.2</td>
<td>51.3</td>
<td>69.4</td>
</tr>
</tbody>
</table>
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 com-
ponent and 1 component; however, 2 or more components of MS increased the OR of KOA significantly (vs no com-
ponent; 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, medi-
al MJSW (mm), lateral MJSW (mm), medial JSA (mm²), lateral JSA (mm²), and OPA (mm²), classified by the num-number of components of MS. The values of medial MJSW tended to be significantly lower, and those of OPA signifi-
cantly 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 MJSW (β = −0.148, R² = 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: β = −0.152, R² = 0.14, p < 0.001; women: β = −0.149, R² = 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 (β = 0.12, R² = 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: β = 0.15, R² = 0.08, p < 0.001; women: β = 0.11, R² = 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, 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 inversely related to the values of medial JSA in women (β = −0.096, R² = 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 factors1,7,8,9,10,11. We have already reported that higher BMI was associated with radiographic KOA based on an analysis using the same population evaluated in our study36, 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 fac-
tors including blood glucose, hypercholesterolemia, and HTN were associated with both unilateral and bilateral KOA and were independent of OW20. Sowers, et al21 defined the presence of ≥ 2 of the following criteria as card-
diometabolic 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-

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.
betes mellitus, and assessed the association between car-
diometabolic clustering and KOA. They found that KOA
was significantly more frequent in obese women with car-
diometabolic clustering compared with those without it. 21.
Using data from the National Health and Nutrition
Examination Survey III (NHANES III), Singh,
et al
sug-
gested 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, hyper-
glycemia, elevated TG, and low HDL cholesterol, was more
prevalent in the population with OA than in the population
without OA22. 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 indi-
cates that, even if the effect of each component of MS on
KOA may be weak, accumulation of the number of compo-
nents 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 com-
ponents of MS. In contrast, OPA values became signifi-
cantly 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 KOA21. 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 estro-
gen 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. 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. It has been hypothesized that atherosclerotic changes and obesity-associated metabolic changes in the subchondral bone are associated with OA. 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. 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. In our study, we adjusted not only for age and sex, but also for values of BMI (men > women), BP (men > women), and HDL cholesterol (women > men). Possibly implicating an involvement of muscle strength to compensate for the mechanical stress, since women are known to have less muscle strength than men. 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. Recent systematic review and metaanalysis of observational studies concluded that there is a sex-dependent association between levels of testosterone and occurrence of MS. 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. 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. In addition, as reported, the prevalence of KOA in Japanese as well as Chinese cohorts is significantly higher than in whites. 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). 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, 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. 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. 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 MS JW 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


Yoshimura, et al: Knee OA risk factors 929

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2011. All rights reserved.


